Phytomedicine 21 (2014) 1349–1355

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.de/phymed

The effects of repeated administration of camphor-crataegus berry extract combination on blood pressure and on attentional performance – A randomized, placebo-controlled, double-blind study

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ARTICLE INFO

Article history:
Received 22 March 2014
Received in revised form 4 May 2014
Accepted 27 June 2014

Keywords:
Camphor
Crataegus berry
Blood pressure
Cognitive function
Complaints

ABSTRACT

The present study investigated the effects of repeated administration of Korodin®, a combination of camphor and crataegus berry extract, on blood pressure and attentional functioning. This study was conducted based on a randomized, placebo-controlled, double-blind design. 54 persons participated (33 female, 21 male) with a mean age of 24.3 years. Blood pressure and body mass index were in the normal range. Participants received 20 drops of either Korodin® or a placebo for four times with interjacent time intervals of about 10 min. Blood pressure was measured sphygmomanometrically before and after each administration. Attentional performance was quantified by using two paper-and-pencil tests, the d2 Test of Attention and Digit Symbol Test.

Greater increases in blood pressure occurred after the four Korodin® administrations in comparison to the four placebo administrations. The performance in two parameters of d2 Test of Attention was consistently superior after the intake of Korodin®. The excellent tolerability and safety of Korodin®, even after a total consumption of 80 drops, was confirmed.

Introduction

The camphor-crataegus berry extract combination, Korodin® Herz-Kreislauf-Tropfen, is widely used for the treatment of low blood pressure. It is applied both during transient phases of hypotension, including orthostatic hypotension, and in patients suffering from chronic hypotension. The latter form of hypotension is relatively widespread, insofar as about 3–5% of the general population is affected (Duschek and Schandry 2007).

Hypotension, including orthostatic hypotension, is associated with significant morbidity and mortality (Mukai and Lipsitz 2002). Furthermore, it has been identified as serious risk factor for stroke and coronary artery disease in the elderly (Eigenbrodt et al. 2000; Jones et al. 2012; Masaki et al. 1998; Rose et al. 2006). Fedorowski et al. (2010) reported an increased risk for cardiac events and all-cause mortality in middle-aged individuals suffering from hypotension. Mattila et al. (1988) showed higher mortality for the subgroup with the lowest blood pressure within the group of individuals above an age of 85 years. Furthermore, an association of low blood pressure in late adolescence with subsequent mortality has been reported (Sundstrom et al. 2011). Additionally, low blood pressure is associated with anxiety and depression (e.g. Hildrum et al. 2007).

Subjective symptoms typically accompany chronically low blood pressure; among these symptoms are fatigue, reduced drive, depressed mood, faintness, dizziness, headache, palpitations, and cold limbs (Weiss and Donat 1982). A considerable impact of these complaints on subjective well-being and quality of life has been shown in several large, population-based studies (e.g. Pilgrim et al. 1992).

In addition to the subjective complaints, several studies have revealed reduced cognitive performance due to chronic hypotension. Wharton et al. (2006) observed deficits in visuospatial attention tasks in persons with low blood pressure and Stegagno et al. (1996) reported reduced performance of hypotensive subjects on a short-term memory test and a mental arithmetic task. As a physiological mechanism mediating the relationship between low blood pressure and cognitive deficits, alterations in cerebral blood flow have been suggested (Owens and O'Brian 1996; Pilgrim et al. 1992).

Treatment of symptoms of low blood pressure has been shown to be effective in several studies applying chemically synthesized antihypotensiva like midodrine (Low et al. 1997) as well as the phytocombination of natural camphor and the extract from fresh

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http://dx.doi.org/10.1016/j.phymed.2014.06.014
0944-7113/

crataegus berry, i.e. Korodin® (Belz and Loew 2003; Duschek et al. 2007; Kroll et al. 2005). For the latter compound it was demonstrated that hypotensive symptoms such as dizziness, vertigo and fatigue could be reliably reduced. In a large multicentre study including 490 patients with orthostatic hypotension Hempel et al. (2005) demonstrated a superior reduction of hypotensive complaints using the camphor-crataegus combination as compared to chemically synthesized antihypotensiva.

Various attempts have been undertaken to investigate the positive effects of pharmacological antihypotensive therapy on mental functioning (Duschek et al. 2007; Schandry and Duschek 2008; Werner et al. 2009). Duschek et al. (2007) were able to show that the application of the relatively long-acting sympathomimetics midodrine and etilefrine lead to increased attentional performance. It was demonstrated that the elevation of blood pressure through Korodin® was accompanied by an improvement of cognitive performance (Schandry and Duschek 2008; Werner et al. 2009).

Studies investigating the effects of antihypotensive drugs on extended time base are rare. Schandry (1999) reported a positive effect on subjective symptoms after 2 weeks of therapy with etilefrine. Hempel et al. (2005) presented data from a retrospective epidemiological cohort study, in which Korodin® was administered. The median of the duration of therapy was 71 days. In 70% of patients symptoms were reduced, in 23% symptoms had disappeared and in 7% symptoms were unchanged. However, because of the retrospective and observational character results of this study are of limited validity. In addition, Harder and Rietbrock (1990) investigated the long-term effects of Korodin® in an open multicentre trial of 4 weeks duration. Participating patients suffered from functional cardiovascular disorders. At the end of the observation period the group-mean of systolic pressure had increased by 5.8 mmHg, and of diastolic blood pressure by 3.2 mmHg. Subjective symptoms, related to the cardiovascular system, had decreased in about 90% of the patients. However, an unequivocal interpretation of the results is not possible because of the lack of randomization and a placebo group.

Relatively little is known about the effects of a repeated administration of Korodin®. A study where Korodin® was administered repeatedly on a comparatively short time basis was reported (Belz et al. 2000; Herrmann et al. 1996). The authors investigated on the basis of a placebo-controlled design the effects of cumulative doses of Korodin® (20, 40, 80, and 120 drops) applied in a regular interval of about 1 h between each dose step. They observed dose-dependent increases in mean arterial pressure after each Korodin® administration and slight rise in the base level of the mean arterial pressure. However, this design does not allow disentangling the pure repetition effect from the dose-dependent effect.

With the present study we aimed to investigate the effects of multiple Korodin® administrations in an unconfounded manner. Blood pressure and parameters of attentional functioning were assessed as dependent variables on the basis of a randomized, placebo-controlled, and double-blind study design.

Materials and methods

Study design

This single centre, double-blind, placebo-controlled, and randomized trial was performed in June 2012. The protocol was approved by the Ethics Committee of the Faculty of Psychology and Education of the University of Munich. The study followed the guidelines of the declaration of Helsinki and Tokyo for humans. Assessments were conducted at the Biological Psychology Research Unit of the University of Munich. The attending physician and research assistant underwent pre-study training. Participants were requested not to smoke, drink alcohol or beverages containing caffeine for 3 h prior to the experimental sessions. Furthermore, they were informed to have breakfast before participating. All participants had to give a written informed consent and received financial remuneration of 50 Euro. The session lasted for about 50 min.

Participants

54 persons, 33 female (61.1%), 21 male (38.9%) participated. Age ranged from 18 to 40 years (mean age: 24.3 years). Recruitment was accomplished by advertisements as well as by information signs posted in several university buildings. Health status of the participants was assessed by anamnestic interview and questionnaire covering diseases of the cardiovascular, respiratory, gastro-intestinal systems, thyroid, liver, as well as metabolic diseases and psychiatric disorders.

Exclusion criteria were presence of affective disorders, serious chronic diseases, history of substance abuse, severe cognitive disorder, pregnancy or breast-feeding.

Randomization and blinding

Verum (Korodin®) and placebo were individually prepared in small brown bottles, provided with a number. The assignments of bottle numbers to subject numbers were to be found on a separate sheet, prepared by the sponsor. Subject numbers were assigned to participants according to the sequence of their appearance. Thus, after assigning the subject number to a participant the corresponding bottle number was evident. Unblinding occurred at data analysis.

Study drugs

Participants of the verum group received four times 20 drops of Korodin® (being purchased in a pharmacy). Hundred grams of Korodin® contain 97.3 g fluid extract from fresh crataegus berries (drug-extract-ratio 1:1.3–1.5; final ethanol concentration 60 vol%), 2.5 g natural D-camphor, and 0.2 g menthol as an aromatic ingredient. One drop Korodin®, a brown clear liquid, contains 38.62 mg crataegus berry extract and 1 mg D-camphor.

Korodin® heart circulation drops are a combination of D-camphor and a liquid extract from fresh hawthorn fruits (crataegi fructus recens) for oral use. The approved indication is hypotonic and orthostatic circulatory dysregulation. Korodin® heart circulation drops are in the current composition as an OTC medicinal product since 1962, exclusively available in pharmacies. Korodin® is on the market in Austria and Germany, where it was originally introduced in 1927.

In the placebo group, 20 drops of wormwood tea (prepared in the investigators lab) was administered four times. This liquid is of a bitter taste similar to Korodin® and is also of brown colour. Both Korodin® and placebo were of brown colour and dispensed on a sugar lump.

Test material

d2 Test of Attention

The d2 Test of Attention (Brickenkamp 1994) measures processing speed, rule compliance, and quality of performance, allowing for an estimation of individual attention and concentration performance. Reliability has proven to be very high, and validity of the technique has been documented by a number of research studies. Two parameters were used in the present study to quantify speed and accuracy of performance: (1) the total number of errors (TE), i.e. skipped targets and erroneously marked distractors, and (2) concentration performance (CL), i.e. number of items