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The Homeopathic Preparation Vertigoheel® Versus *Ginkgo biloba* in the Treatment of Vertigo in an Elderly Population: A Double-Blinded, Randomized, Controlled Clinical Trial

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ABSTRACT

Objective: Alternative medical practices are common in the treatment of vertigo. This study compared the effects of *Ginkgo biloba* treatment with the homeopathic remedy Vertigoheel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany).

Design: Randomized, double-blinded, parallel group study.

Subjects: One hundred and seventy (170) patients, ages 60–80 years, with atherosclerosis-related vertigo.

Interventions: Patients were randomly allocated to receive treatment with either Vertigoheel ($n = 87$) or *G. biloba* ($n = 83$).

Outcome measures: The results were analyzed for the non-inferiority of Vertigoheel to *G. biloba* on the combined endpoint of changes from baseline to week 6 in dizziness score (assessed by questionnaire), frequency, duration, and intensity of vertigo episodes (recorded in patient diaries).

Results: Both treatments improved vertigo status. From a baseline mean value of 26.1 ± 5.2 (on a 50-point scale) in the Vertigoheel group, the dizziness questionnaire score improved by −10.6 ± 10.0, and by −10.7 ± 9.0 from 25.8 ± 4.7 in the *G. biloba* group. Statistical analysis of this endpoint showed that Vertigoheel was not inferior to *G. biloba*. The 95% confidence interval for the difference between treatment did not reach the inferiority threshold of 0.36 at any of the time points tested. The results were supported by the results of a line walking test, Unterberger's stepping test, and patient and physician global assessments of therapeutic effect. Both treatments were well tolerated.

Conclusions: Vertigoheel is an appealing alternative to established *G. biloba* therapy for atherosclerosis-related vertigo.

INTRODUCTION

Vertigo is a commonly occurring condition that has a serious impact on sufferers' quality of life. Vertigo is defined as a false sensation that oneself or the surroundings are moving or spinning, and is usually accompanied by nausea and loss of balance (Daroff et al., 2001). It is common for vertigo sufferers to experience emesis, sweating, tinnitus, and collapse, all of which contribute to anxiety. Moreover, the disruption of natural equilibrium, resulting in imbalance and instability, can have a serious impact on patients' professional and social lives.

Vertigo can be caused by a variety of disorders, most frequently by disturbances of the inner ear structures such as the vestibular nerve or the vestibular cochlear system (vestibular vertigo). Disorders affecting the brain stem and

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cerebellum (such as vertebrobasilar insufficiency following transient ischemic attack) can also cause vertigo. Other causes include Meniere's disease, bacterial or viral infections, Paget's disease, tumors, inflammation of or damage to nerves, increased pressure within the skull, or the use of drugs that affect the inner ear, including aminoglycoside antibiotics, aspirin, cisplatin, and furosemide.

Most pharmacologic interventions used to prevent or to treat vertigo are antihistamines (Daroff et al., 2001). These drugs have been associated with side effects, such as drowsiness and dry mouth, especially in elderly patients. Moreover, they can cause agitation in very young children and infants. Possibly because of these tolerability issues, vertigo is widely treated with alternative medical practices.

The interest in such practices, particularly homeopathy, has grown rapidly in recent years (Haltenhof et al., 1995; Knipschild et al., 1990; Schüppel and Schlich, 1994). However, as the use grows, the need for sound clinical research into alternative practices becomes more pressing.

Here we report the findings of a prospective, randomized, controlled, 8-week, double-blinded trial of the homeopathic preparation Vertigoheel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany) in the treatment of vertigo. The aim of the study was to demonstrate that Vertigoheel is noninferior to phytotherapy with *Ginkgo biloba* extract (Dr Willmar Schwabe GmbH, Germany) in elderly patients with atherosclerosis-related (specifically cerebral) vertigo. *G. biloba* is registered as a drug in Germany and several other European countries. *G. biloba* has been shown to have a superior efficacy profile and good tolerability compared with placebo in studies of vestibular and nonvestibular vertigo (Hamann, 1985).

PATIENTS AND METHODS

Patients

Caucasian patients between the ages of 60 and 80 years were enrolled at 13 study centers (clinics practicing either alternative medicine or both alternative and conventional medicine) in Germany. Eligible patients had previously diagnosed vertigo or at least one of the following symptoms of vertigo: blackouts, unsteadiness, grogginess, lightheadedness, torpor, "seeing stars," or flickering, blurred, or impaired vision. The primary inclusion criteria included the occurrence of at least 3 episodes of vertigo per day in the week prior to the study or constant vertigo, with a median intensity of vertigo episodes between 2 and 4 on a 5-point assessment scale; a total score of at least 20 in a specially designed dizziness questionnaire; a score of at least 20 points in the Tinetti mobility test; and no aural impediments. Patients were also required to have normal blood pressure at enrollment (systolic between 110 and 160 mm Hg, diastolic between 70 and 90 mm Hg).

Exclusion criteria included participation in another clinical study within 30 days prior to enrollment; lactose intolerance; known serious chronic or malignant disease or neurologic disorders; treatment with an antivertigo agent, antiemetic, corticosteroid, agent affecting circulation, antihistamine, migraine medication, streptomycin, gentamycin sedatives, or psychoactive medication in the 7 days prior to the study; or anticoagulation therapy (including salicylate) in the 4 weeks prior to the start of the study.

All patients provided written informed consent. The study protocol (and two amendments) were approved by the independent ethics committees at each of the study centers and the study was conducted according to the good clinical practice (GCP) guidelines and the Declaration of Helsinki and its amendments (World Medical Association, 2002).

Study design

This was a randomized, double-blinded, parallel group study. At visit 1 (day 1), patients were randomly allocated to receive treatment with two tablets of Vertigoheel t.i.d. or one tablet of *G. biloba* extract plus one placebo tablet t.i.d. for 8 weeks. All tablets were of similar size and color. One tablet of Vertigoheel contains 210 mg of cocculus D4, 30 mg conium D3, 30 mg ambra D6, and 30 mg of petroleum D8. The *G. biloba* tablets contain 40 mg of dried extract from *G. biloba* leaves standardized to 24% ginkgo flavone glycosides and 6% terpene lactones. At visit 2 (day 15 ± 2), visit 3 (day 29 ± 3), visit 4 (day 43 ± 3), and visit 5 (day 57 ± 4), efficacy assessments were performed, patient diaries checked, concomitant medication recorded, and adverse events were noted. At the final visit, a physical examination was performed, blood pressure and heart rate checked, physician and patient global assessment of efficacy and tolerability were recorded, patient diaries and remaining study medication were returned to the investigator, and an assessment of compliance was performed.

The primary variable was evaluated after 6 weeks of treatment (visit 4). This was a combined endpoint including assessment of overall quality of life, and mean daily frequency, intensity, and duration of vertigo episodes (recorded in a patient diary). Duration was assessed on a five point scale (0 to 4) where 0≤2 minutes and 4 = continuous vertigo. Secondary endpoints included the total score and physical and psychological subscores in the dizziness questionnaire; mean daily frequency, duration, and intensity of vertigo episodes over 8 weeks (on a 5-point scale, 0 = none to 4 = very strong); overall therapeutic effect (patient and physician assessments); attempts at walking a line; and Unterberger's stepping test (assessed on a scale of very good, good, moderate, poor, unsuccessful). Safety was evaluated by monitoring adverse events and overall assessment of tolerability (patient and physician assessments). Compliance was assessed as the percentage of planned dosage of tablets or capsules taken by the patients in each group.

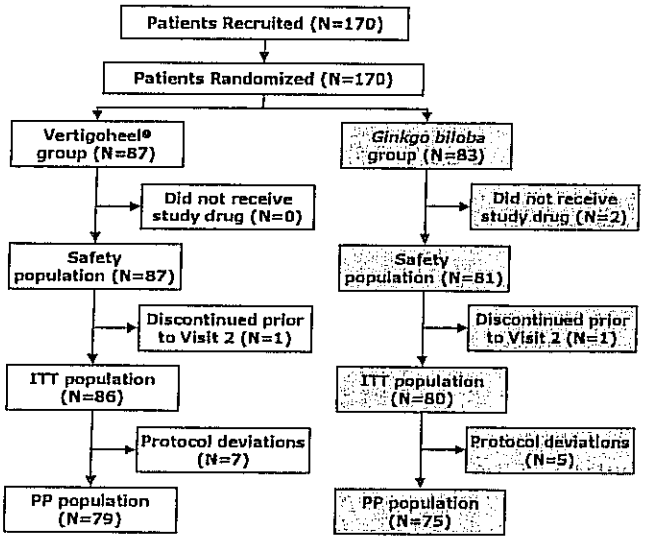

FIG. 1. Flow chart of patient disposition. Vertigoheel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany). ITT, intention-to-treat; PP, per protocol.

Statistical methodology

The intent to treat (ITT) population included all randomized patients who received study medication and attended at least one study visit after the start of treatment. The per protocol (PP) population was made up of patients who received treatment for 2 weeks or more, took between 80% and 110% of the planned doses of study medication, and remained in the study beyond visit 4 or had previously discontinued because of resolution of vertigo or unsatisfactory therapeutic effect. Safety and compliance were evaluated in all randomized patients by recording the frequency, severity, and relationship with study medication of all adverse events. The primary analysis of efficacy was performed in the PP population and the safety analysis in the safety population.

Mean change from baseline was calculated using entries from patient diaries in the 7 days prior to visit 2 (week 2), visit 3 (week 4), and visit 4 (week 6). A combined test for all 4 criteria was performed. The test was the directional test of the generalized Wilcoxon-Mann-Whitney procedure as described (Lachin, 1992; Wei and Lachin, 1984). The relevance of the difference between Vertigoheel and *G. biloba* was measured using the Mann-Whitney statistic $P(X < Y)$, a measure of stochastic superiority with benchmarks, analogous to the Cohen effect size (Colditz et al., 1988). The test of noninferiority ("equivalent" or "better") was performed by means of a one-sided 95% confidence interval (CI). If the lower boundary of the CI > 0.36, the null hypothesis of inferiority could be rejected. The level of significance was set to $p = 0.05$.

Secondary endpoints were analyzed using the Mann-Whitney test. Safety data were analyzed using descriptive statistics. Compliance was assessed at week 8 and was also analyzed with descriptive statistics.

RESULTS

Study population

A total of 170 patients were enrolled. The patient disposition is shown in Figure 1. Seven (7) patients in the Vertigoheel group and 5 in the *G. biloba* group were not included in the PP analysis (because of violation of inclusion/exclusion criteria, administration of prohibited concomitant medication, poor compliance, or making visit 4 outside the specified time window).

Baseline characteristics of the ITT population were not significantly different between the patients groups. Data for

TABLE 1. MEAN DEMOGRAPHIC AND BASELINE CHARACTERISTICS

	Vertigoheel®[a] *(n = 79)*	Ginkgo biloba *(n = 75)*	p
Age (years)	69.6 ± 5.9	69.4 ± 5.9	0.81[b]
Body weight (kg)	73.0 ± 12.4	74.8 ± 10.8	0.22[b]
Height(cm)	165.2 ± 7.8	167.2 ± 8.4	0.07[b]
Gender (% male)	25.3	41.3	0.04[c]
Smokers (%)	24.1	21.3	0.81[c]
Alcohol drinkers (%)	55.7	56.0	0.99[c]
Dieters (%)	15.2	12.0	0.64[c]
Time since diagnosis (years)	3.3 ± 5.3	3.2 ± 4.6	0.28[b]
Tinetti's mobility test score	24.9 ± 2.3	24.9 ± 2.1	0.90[b]
Line walking score (%)	86.2 ± 15.8	87.9 ± 13.9	0.26[b]
Unterberger's stepping test score	28.4 ± 32.6	25.7 ± 31.1	0.34[b]

[a]Biologische Heilmittel Heil GmbH, Baden-Baden, Germany.
[b]Wilcoxon rank test.
[c]Fisher's exact test.

TABLE 2. PRIMARY ENDPOINT RESULTS: SUMMARY OF DIZZINESS QUESTIONNAIRE SCORES AND FREQUENCY, DURATION, AND INTENSITY OF VERTIGO EPISODES

	Vertigoheel®[a] (n = 79)		Ginkgo biloba (n = 75)		*Difference between Vertigoheel and* Ginkgo biloba
	Mean value	*Change from baseline*	*Mean value*	*Change from baseline*	
Dizziness questionnaire score[b]					
Baseline	26.1 ± 5.2		25.8 ± 4.7		
Week 6	15.5 ± 9.7	−10.6 ± 10.0	15.1 ± 9.0	−10.7 ± 9.0	−0.1 ± 9.5
Mean frequency of episodes per day over last 7 days					
Baseline	6.4 ± 5.5		5.6 ± 4.7		
Week 6	2.1 ± 3.5	−4.2 ± 5.3	2.5 ± 4.0	−3.1 ± 3.9	1.1 ± 4.7
Duration of episodes score[c]					
Baseline	1.8 ± 1.4		1.7 ± 1.3		
Week 6	0.7 ± 1.1	−1.1 ± 1.3	1.1 ± 1.2	−0.6 ± 1.1	0.4 ± 1.2
Intensity of episodes score[d]					
Baseline	2.4 ± 0.5		2.4 ± 0.6		
Week 6	1.0 ± 0.7	−1.4 ± 0.8	1.2 ± 0.8	−1.2 ± 0.8	0.2 ± 0.9

[a]Biologische Heilmittel Heel GmbH, Baden-Baden, Germany.
[b]0 = no dizziness, maximum dizziness = 50.
[c]0 = 0–2 mins, 1 = 2–10 mins, 2 = 11–60 mins, 3 > 1–6 hours, 4 = continuous vertigo.
[d]0 = none, 1 = light, 2 = moderate, 3 = strong, 4 = very strong.

the PP population are shown in Table 1. The mean age of the study population was 69.5 years. In the Vertigoheel group, only 25.3% of patients were male versus 41.3% in the *G. biloba* group; this difference was statistically significant. The most common vertigo symptoms were dizziness (64.6% in the Vertigoheel group versus 60.0% in the *G. biloba* group), unsteadiness (58.2% versus 70.7%), grogginess (43.0% versus 45.3%), and torpor (45.6% versus 50.7%).

Improvement in vertigo status

As this was a noninferiority study, a conservative per-protocol analysis was used. An ITT analysis was performed with no essential differences compared with the PP analysis. The primary-endpoint analysis showed that Vertigoheel was noninferior to *G. biloba* in the treatment of vertigo in this population (Table 2, Fig. 2). The evolution of scores in the dizziness questionnaire was almost identical in both treatment groups over the course of the study (Fig. 3).

Improvements were also observed from baseline to week 6 in the frequency, duration, and intensity of vertigo episodes as recorded in the patient diaries. Assessment of the frequency, duration, and intensity of vertigo episodes over the course of the study showed a slight trend towards superiority of Vertigoheel over *G. biloba* (Fig. 4). Im-

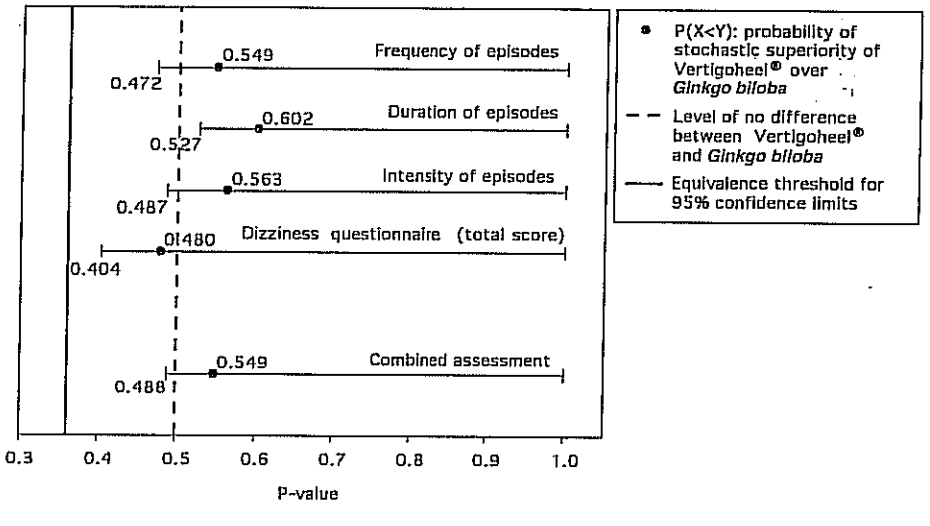

FIG. 2. Primary endpoint: Noninferiority of Vertigoheel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany) and *Ginkgo biloba*.

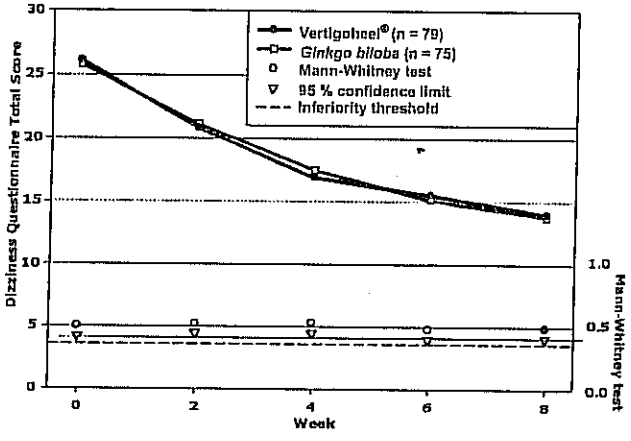

FIG. 3. Dizziness questionnaire scores over time.

provements in line walking were comparable in the Vertigoheel and *G. biloba* treatment groups (mean increases from baseline, 8.0 ± 12.9% in the Vertigoheel group versus 6.6 ± 12.6% in the *G. biloba* group), as were improvements in Unterberger's stepping test and rotation (mean rotation at week 8 was 13.6 ± 19.9° and 13.4 ± 19.1° in the Vertigoheel and *G. biloba* groups, respectively).

The combined test indicated Vertigoheel to be slightly superior to *G. biloba* at $p = 0.05$. The lower boundary of the CI was 0.488, which was also above the noninferiority boundary of 0.36. The lower 95% CI for the difference between treatment did not reach of the inferiority threshold of 0.36 at any of the timepoints tested. All lower boundaries of the CI for individual components were above the inferiority threshold, e.g. noninferiority of Vertigoheel could be shown descriptively.

There was no difference, in terms of treating the psychological or physical symptoms of dizziness, between Vertigoheel and *G. biloba* at any timepoint in the study.

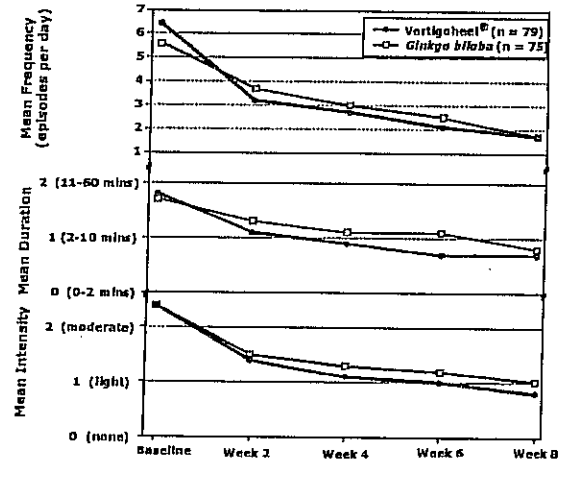

FIG. 4. Evolution of mean frequency, duration, and intensity of vertigo episodes over time.

Global assessment of therapeutic effect and compliance

Global assessments of therapeutic effect by patients and physicians revealed no noteworthy differences between Vertigoheel and *G. biloba* treatments. A greater proportion of patients in the Vertigoheel group (24.1%) than in the *G. biloba* group (16.0%) rated their medication "very good." This was supported by the physician assessments, where values of 25.3% (Vertigoheel) and 17.3% (*G. biloba*) were recorded. Patient and physician assessments were consistent (within 5%) in each category. Compliance was excellent in both treatment groups with values of 96.9 ± 4.2% for tablets and 97.5 ± 4.6% for capsules in the Vertigoheel group compared to 98.2 ± 3.7% and 98.1 ± 4.2% in the *G. biloba* group.

Tolerability

Both treatments were well tolerated. Only one adverse event in the Vertigoheel group was reported to have a suspected relationship to the study medication (abdominal pain and nausea). Two such cases were reported in the *G. biloba* group (abdominal pain and flatulence, and dermatitis). Two serious adverse events occurred, but neither was treatment-related: one patient was diagnosed with a pancreatic carcinoma, and one femoral fracture, the result of an accident.

Both treatments had excellent global assessments of tolerability by both patients and physicians. The proportion of patients who rated the tolerability of the study medication as "very good" was 88.5% in the Vertigoheel group compared to 79.0% in the *G. biloba* group. This was supported by the physician assessments, where values of 92.0% (Vertigoheel) and 81.5% (*G. biloba*) were observed.

DISCUSSION

This study shows that the homeopathic preparation Vertigoheel is noninferior to the widely used neurological stimulant, *G. biloba*, in the treatment of elderly patients with atherosclerosis-related vertigo. This was shown in an analysis of the combined primary endpoint of dizziness questionnaire score and frequency, duration, and intensity of vertigo episodes as recorded in patient diaries. The conclusion was supported by the results on the secondary variables. Both treatments had an excellent tolerability profile and compliance rates were >95% in both treatment groups. These data add to a growing body of evidence on Vertigoheel as a useful and well-tolerated treatment option for elderly patients with vertigo of various origins (Colditz et al., 1988; Strösser and Weiser, 2002; Weiser et al., 1998; Wolschner et al., 2001; Zenner et al., 1992).

The mechanism of action of Vertigoheel is not yet known. The preparation contains *Cocculus indicus* (Indian cockles); *Conium maculatum* (spotted hemlock); *Ambra grisea* (am-

bergris), and homeopathically attenuated petroleum. Cocculus and Conium are neurostimulating agents usually indicated for vertigo, nervous disorders, and nausea, whereas homeopathically attenuated petroleum is used in cases of gastritis and is thought to reduce vertigo-associated nausea. Ambergris is a nervous system stimulant and is commonly used for central and autonomic disorders (Metzger, 1964). The principal effects of the preparation have been attributed to the alkaloid coniine (in Conium) (Claussen et al., 1984). It is not clear whether the low concentration of the constituents excludes a direct pharmacologic action of the active agents. In view of the growing body of efficacy data, further studies on the mechanisms of action of Vertigoheel appear warranted.

A potential weakness of the study is in the gender imbalance between the treatment groups: ~25% of patients in the Vertigoheel group were male, compared to >40% in the *G. biloba* group. We do not believe, however, that there is any rationale for attributing the results to such demographic differences.

With the exception of the vertigo questionnaire, the scoring systems used in this study have been used in earlier trials with apparent good reproducibility and can be seen as representing a standardized approach to the evaluation of vertigo status (Weiser et al., 1998; Weiser and Strösser, 2000; Wolschner et al., 2001). The consistency of the results across different variables further supports the reliability of the results, although the possibility of subjective bias on the side of both patient and practitioner should be acknowledged. In the current randomized, double-blinded study, such bias should be evenly distributed between treatment groups, but in open-label studies this risk might be greater. A large-scale evaluation of vertigo scoring systems would be a welcome tool for further research.

In conclusion, the study demonstrated that Vertigoheel was not inferior to *G. biloba* extract, in terms of reducing dizziness, and frequency, duration, and intensity of vertigo episodes, over 6 weeks of treatment in elderly patients with atherosclerosis-related vertigo.

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