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Microcirculatory effects of a homeopathic preparation in patients with mild vertigo: an intravital microscopic study

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Abstract

The effects of the homeopathic preparation Vertigoheel on variables related to microcirculation were investigated using vital microscopy techniques in patients with vestibular vertigo. In a non-randomized, open study, 16 patients given Vertigoheel were compared with 16 untreated patients. Measurements were carried out in two areas (defined by selecting 60 blood-cell perfused nodal points of arterioles, venules, and capillaries with a mean diameter ≥40 μm): the cuticulum/subcuticulum of the inside left lower arm and an area 5 mm behind the left earlobe. After 12 weeks of treatment, patients receiving the homeopathic preparation exhibited an increased number of nodal points, increased flow rates of erythrocytes in both arterioles and venules, increased vasomotion, and a slight reduction in hematocrit vs. baseline. None of these changes were observed in the control group and the differences between treatment groups were statistically significant. Partial oxygen pressure increased significantly in the Vertigoheel group compared with the control group. In addition, in Vertigoheel patients, significantly increased numbers of cell-wall adhering leucocytes were observed, accompanied by increased local concentrations of the adhesion molecules ICAM-1. The microcirculatory changes were associated with a reduction in the severity of vertigo in the actively treated patients, both as assessed by the treating physician and by the patients themselves. The data support a pharmacological effect on microcirculation from the treatment.

Keywords: Homeopathy; Vertigo; Blood flow; Vital microscopy; Immunomodulation

Introduction

Vertigo is a commonly occurring condition defined as light-headedness or a false sensation of moving or spinning. Most cases of vertigo occur with nystagmus, an abnormal, rhythmic, jerking eye movement. Emesis, sweating, tinnitus, and collapse may also occur (Dieterich, 2004; Medline Plus Medical Encyclopedia, 2004).

Frequently used medications for the symptomatic treatment of mild vertigo include meclizine, dimenhydrinate, promethazine, scopolamine, atropine, and diazepam (Daroff and Martin, 2001). Also, the increasing popularity in recent years of complementary medical practices is reflected in a widening use of these strategies for symptomatic treatment of mild vertigo of various etiology (Haltenhof et al., 1995; Knipschild et al., 1990; Schröder et al., 2003). Among reasons for this development may be tolerability concerns with conventional medications or the closer patient–practitioner interactions and more personalized treatments associated with complementary practices such as homeopathy (Schröder et al., 2003).

Whatever the reasons for the increased interest in alternative medicine among both the public and in the medical profession, the widespread use of non-conventional medications has increased the need for scientific data on the agents. A growing number of studies are addressing the effectiveness and tolerability of medications, as well as seeking to gain insight into possible mechanisms by which alternative medications may work. There has been a long-standing debate about whether alternative medications have

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effects beyond those of placebo, with at least one thorough meta-analysis of clinical trials reporting real benefits that cannot be explained by a placebo effect (Linde et al., 1997), which indicates that more than social and psychological factors are involved. However, mechanistic data are lacking and our knowledge of the modes of action of most alternative medications is incomplete.

The current report describes an investigation into the effects of the homeopathic preparation Vertigoheel® (Heel GmbH, Baden-Baden, Germany) on variables related to microcirculation of the vestibular area. Vertigoheel is a mixture of diluted extracts from the plants *Cocculus indicus* (Indian cockles); *Conium maculatum* (spotted hemlock); *Ambra grisea* (ambergris) and homeopathically attenuated petroleum. Vertigoheel is available over the counter in many countries and the components are listed in the Pharmacopeia of the United States (The Homeopathic Pharmacopoeia of the United States (HPUS), 1979).

The interest in evaluating alternative medical practices in a more rigorous manner is reflected in a number of controlled studies on the effects of Vertigoheel since 1998. Benefits in patients with vertigo of various origins have been demonstrated in a number of studies of different design (Claussen et al., 1984; Daroff and Martin, 2001; Wolschner et al., 2001), but there are few data on possible mechanisms of action for this preparation.

We speculated that improvements of the microcirculation in the inner ear with treatment might be a reason for observed symptomatic improvements with the homeopathic preparation. As a proxy for inner-ear circulation in this pilot study, we used an area 5 mm behind the left earlobe. Using a vital microscopic setup, effects on microcirculation were monitored in patients with mild vertigo of systemic vestibular origin on such variables as local blood flow and the number of nodules in microvessel networks, as well as on the possible local immunomodulatory influences by treatment.

Methods

Patients and treatment

This non-randomized, open study included 18 men and 14 women aged 60–70 years. All patients were outpatients at the otorhinolaryngology clinic in Berlin-Buch with evidence of systemic vestibular vertigo as diagnosed by a physician and with at least one of the following symptoms: blackouts, unsteadiness, grogginess, light-headedness, torpor, 'seeing stars', flickering vision, blurred or impaired vision. Patients were not allowed treatment with the study medication for the current symptoms before enrolment into the study, although most participants had received previous therapy (complementary or conventional) for vertigo with little or no success. Patients in the Vertigoheel group (n = 16) were given orally administered Vertigoheel as tablets at a dosage of 2 tablets twice daily for a total of 12 weeks. The control group did not receive matching placebo. In addition, all patients received physiotherapy for vertigo but no further medication was administered. All patients gave their informed consent.

Clinical variables

Data on the clinical effects of the therapy were analyzed at monthly intervals. Severity of vertigo was determined on horizontal nystagmus in 9 lines of vision. Additionally, patients were asked at the end of the study on week 12 to evaluate the degree of change in their condition on a scale from 1 to 5 where 1 represented a clear deterioration of symptoms, 3 no change, and 5 a clear improvement of symptoms. Compliance was evaluated by the practitioners as low, moderate, good, and very good. Tolerability was evaluated as the occurrence of patient-reported adverse events.

Analysis of microcirculation

The experimental setup used for the analysis of microcirculation has been described previously (Klopp et al., 1996, 2000). Briefly, the system uses an intravital microscope equipped with a combined reflected/transmitted light system, with selective light sources and selective filters. The microscope uses a distance-objective (working distance 3–8 mm), a vertical zoom and horizontal-scan tube. Images were obtained under defined illumination and filter conditions (special distribution of reflected and transmitted light components, radiation characteristics, incidence angle of reflected light, and filtering of reflected and transmitted components). The primary images were processed with a KONTRON computerized image construction and processing system. A block diagram of the setup is shown in Fig. 1.

Each microscopic examination was carried out with the patient in a sitting position at the same time (9–11 a.m., 3–5 p.m.) after 2 h of acclimatization, under constant ambient temperature. Data were compared statistically at the following measurement times: Week 0 (baseline values), weeks 4, 8, and 12. Two target areas were selected for measurements: the cuticulum/subcuticulum of the inside left lower arm (area A) and an area 5 mm behind the left earlobe (area B). Each area of analysis was defined by selecting 60 blood-cell perfused nodal points of arterioles, venules, and capillaries with a mean diameter $\geq$40 μm. Branches were defined as 'blood-cell perfused' if they had an erythrocyte boundary flow velocity of around 80 μm/s over a period of at least 20 s. The interconnected microvessel networks were analyzed in a target volume of 1 mm^3.

Variables were monitored by a frame-by-frame analysis of the primary images, which were documented on instant micrographs with exposure times up to 1/8000 s, on videotape and on high-speed 35 mm cinefilm with up to 120 exposures/s. The following variables were analyzed: percentage change from initial conditions in existing blood-

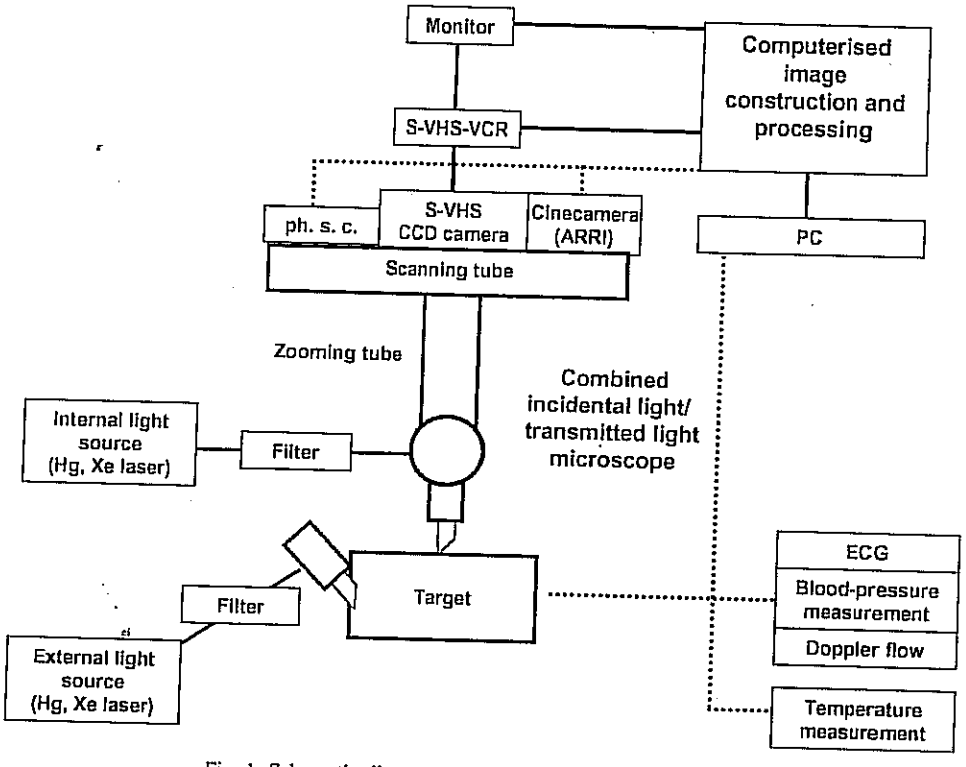

Fig. 1. Schematic diagram of the intravital microanalysis setup.

cell perfused nodal points in the network of microvessels; flow rates of erythrocytes in arterioles and venules; arteriolar and venular vasomotion (considered as complex oscillations and quantified as the area under the curve of an amplitude-frequency spectrum); number of leukocytes adhering to a defined wall of a venule (18,000 μm^2); and tube hematocrit. Further, changes in local concentrations of intercellular adhesion molecule 1 (ICAM-1) were measured with reflexion microscopy (SPEX) as described previously (Klopp et al., 2001, 2002) and the change in partial oxygen pressure in the tissue was monitored using a CLARK electrode.

Data were analyzed statistically, assuming normal distribution of data, by means of a *t* test and Wilcoxon's rank-sum test at a 5% significance level.

Results

The study included 18 men and 14 women, 16 of whom received Vertigoheel. All patients received physiotherapy for vertigo. Patients were matched for age (66.4 ± 3.1 vs. 65.6 ± 2.8 years in the Vertigoheel and control groups, respectively), weight, and height.

Findings on microcirculation variables

There were significant differences between the treatment groups in all the microcirculation variables studied. For all variables, the differences started to appear at Week 4 and differences increased during the course of the study.

In the Vertigoheel group, the number of blood-cell perfused nodal points in the network of microvessels increased from 60 at baseline to 64.5 ± 3.1 (all values are means ± SD) in area A and to 66.1 ± 4.1 in area B. No changes from baseline to the end of study were reported for the control group (Fig. 2). The differences between treatment groups were statistically significant. The flow rates of erythrocytes increased with Vertigoheel in both arterioles (from 2.1 ± 0.1 to 2.3 ± 0.2 $\mu m^3/s$ and from 2.2 ± 0.1 to 2.3 ± 0.2 $\mu m^3/s$ in areas A and B, respectively; Fig. 3, left-hand panel) and venules (from 2.1 ± 0.1 to 2.3 ± 0.2 $\mu m^3/s$ and from 2.1 ± 0.1 to 2.3 ± 0.2 $\mu m^3/s$ in areas A and B,

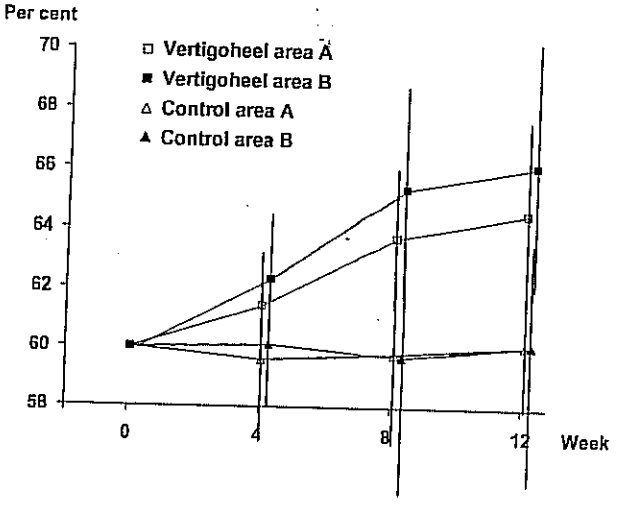

Fig. 2. Number of nodal points at different time points for the Vertigoheel and control groups, respectively. Squares represent data for the Vertigoheel group; triangles are control. Lines indicate SD.

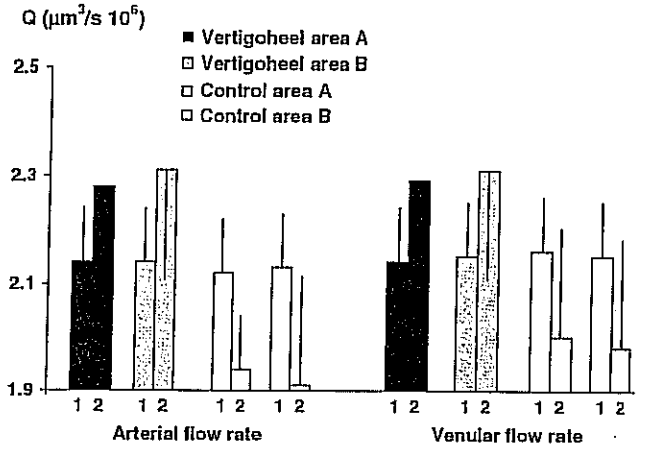

Fig. 3. Arterial (left) and venular (right) flow rates in patients treated with Vertigoheel or control at baseline (bars 1) and end of study (bars 2). Lines indicate SD.

respectively; Fig. 3, right-hand panel). In the control group, arteriolar flow rates decreased slightly (from 2.2 ± 0.1 to 2.0 ± 0.2 µm³/s and from 2.2 ± 0.1 to 2.0 ± 0.1 µm³/s in areas A and B, respectively; Fig. 3, left-hand panel) and venular flow rates decreased in both target areas (from 2.1 ± 0.1 to 1.9 ± 0.2 µm³/s and from 2.1 ± 0.1 to 1.9 ± 0.2 µm³/s in areas A and B, respectively; Fig. 3, left-hand panel). All differences between groups were statistically significant. Vasomotion also improved in the Vertigoheel group whereas there was no change from baseline in patients in the control group. In the Vertigoheel group, vasomotion increased by 7.5% ± 3.6% and 7.7% ± 4.1% in areas A and B, respectively; in contrast, values in the control group decreased by 2.1% ± 5.8% and 2.3% ± 6.5% (Fig. 4). The number of leukocytes adhering to a defined wall of a venule increased from 0.8 ± 0.8 to 4.7 ± 2.6 and from 0.9 ± 0.9 to 5.8 ± 3.1 in the Vertigoheel group, areas A and

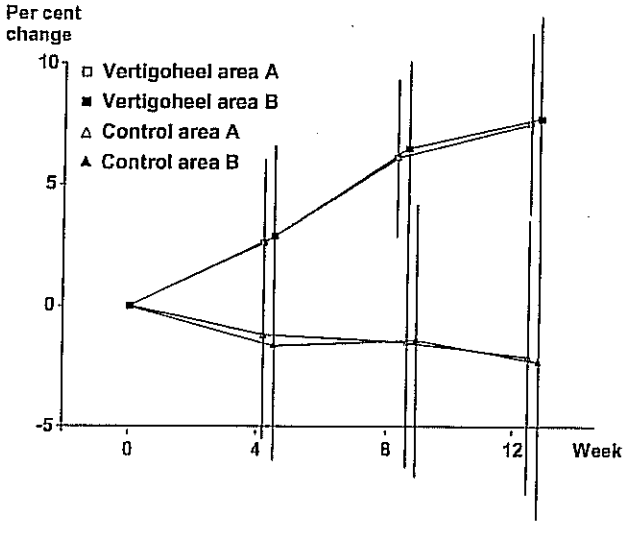

Fig. 4. Per cent change in vasomotion during the course of treatment in the Vertigoheel and control groups, respectively. Squares represent data for the Vertigoheel group; triangles are control. Lines indicate SD.

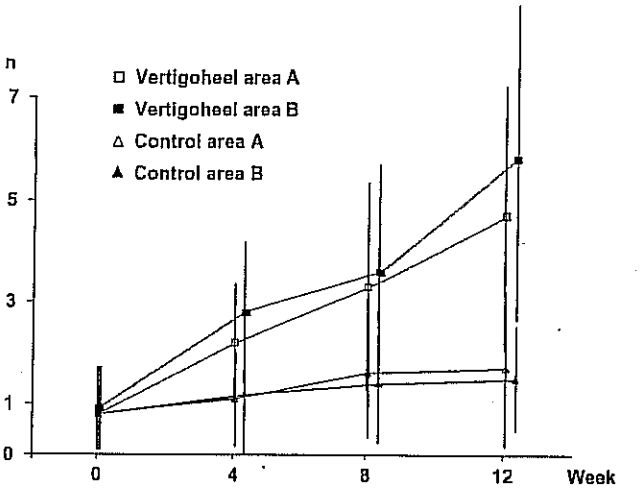

Fig. 5. Number of adhering leucocytes at different time points in the Vertigoheel and control groups, respectively. Squares represent data for the Vertigoheel group; triangles are control. Lines indicate SD.

B, respectively, but there was no increase in the control group (baseline value 0.8 ± 0.8 in both areas, end of study values 1.7 ± 1.5 in area A and 1.5 ± 1.0 in area B; Fig. 5).

Tube hematocrit (Fig. 6) was reduced slightly with Vertigoheel during the course of the study and there was a small increase in the control group (Vertigoheel group decrease by 7.7% ± 5.0% and 8.1% ± 4.9% in areas A and B, respectively; control group increase by 2.4% ± 6.8% and 2.0% ± 6.9% in areas A and B, respectively; between-group differences significant; within-group differences not significant).

Further, there were significantly greater changes in local concentrations of ICAM-1 with Vertigoheel treatment than without therapy (Fig. 7). Expressed in relative units,

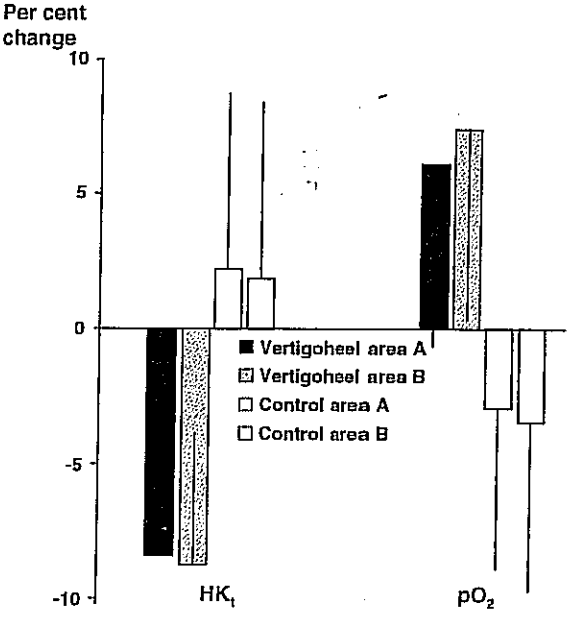

Fig. 6. Per cent change from baseline in tube hematocrit (left) and partial oxygen pressure (right) in the Vertigoheel and control groups in areas A and B, respectively. Lines indicate SD.

ICAM-1 levels increased from 0.4 ± 0.5 at baseline to 3.5 ± 1.8 and 3.7 ± 2.1 in the Vertigoheel group (areas A and B, respectively) but from 0.4 ± 0.5 to 1.3 ± 1.2 and from 0.4 ± 0.6 to 1.4 ± 1.5 in the control group. The change from baseline in the control group were not statistically significant; however, the changes from baseline in the Vertigoheel group were significant, as were changes relative to the control group.

Partial oxygen pressure increased in the Vertigoheel group during the course of the study, in both tissue areas evaluated (Fig. 6). In patients receiving Vertigoheel, partial oxygen pressure increased from baseline by 6.1% ± 7.0% and 7.4% ± 7.3% in areas A and B, respectively. In the control group, partial oxygen pressure was reduced from baseline to the end of study by 2.9% ± 5.8% and 3.4% ± 6.4% in the two target regions. As with the other study variables, the differences between treatment groups at end of treatment were significant, but the differences between the target areas in each subject group were not.

A representative micrograph showing the states of the microcirculatory network at baseline and after 12 weeks of treatment is shown in Fig. 8.

Clinical effects and tolerability

There were greater improvements in the severity of vertigo evaluated on horizontal nystagmus in the Vertigoheel patient group than in the control group. Symptoms started to improve in the Vertigoheel group between Weeks 4 and 8 and the differences between treatment groups at the end of the study were statistically significant. Patients' own evaluation of symptoms at the end of the study reflected the severity data: 8 patients receiving Vertigoheel reported clear improvements in symptoms with treatment at Week 12; no patient in the control group reported similar improvements (Table 1). These differences between treatment groups were statistically significant.

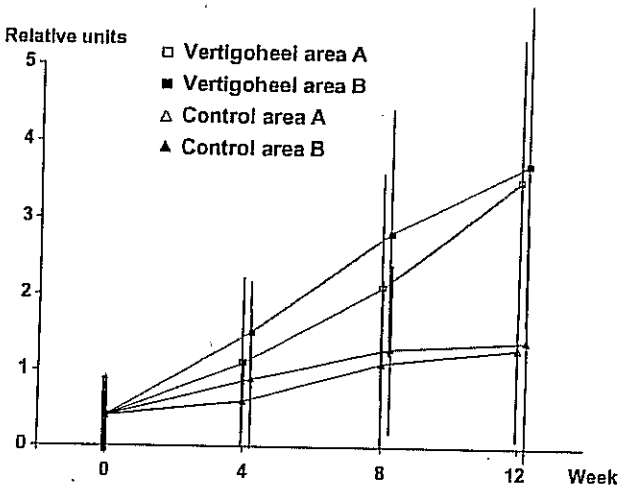

Fig. 7. Local concentrations of ICAM-1 cells (relative units) at different time points in the Vertigoheel and control groups, respectively. Squares represent data for the Vertigoheel group; triangles are control. Lines indicate SD.

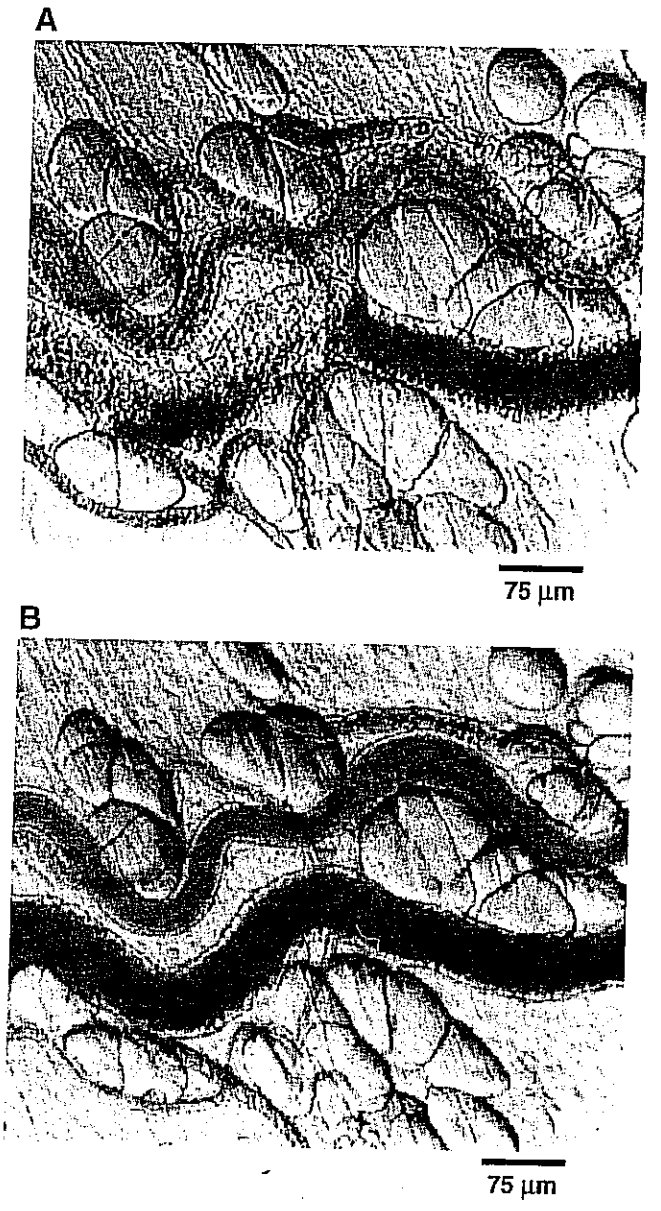

Fig. 8. Intravital micrographs showing a representative example of the state of the vessel network in area A at baseline (A) and after 12 weeks of treatment with Vertigoheel (B). The scale bar represents 75 µM.

Tolerability was very good in all patients receiving Vertigoheel. No adverse events were reported and all practitioners graded compliance with the study medication as 'very good'.

Table 1
Change in symptoms assessed by patients at the end of the study compared with baseline

	Vertigoheel (*n*)	Control (*n*)
Clear improvement	8	0
Some improvement	5	3
No change	3	11
Some deterioration	0	3
Marked deterioration	0	0

Discussion

This work reports effects on markers of microcirculatory function from treatment with a homeopathic preparation, Vertigoheel, in patients with mild systemic vertigo. The changes observed with active treatment compared with control may add to our understanding of the mode of action of this remedy and support the case for a real pharmacological effect of the preparation. Complementary medical practices are becoming increasingly popular and the reasons given for this support are manifold. Pharmacological efficacy is sometimes given as less of an explanation than such factors as the closer patient–practitioner interactions and more personalized treatments associated with complementary practices than with conventional practices (Schröder et al., 2003). The current data support the efficacy argument.

Certain limits of the study should be admitted up front. As a proxy for inner-ear circulation, we used an area 5 mm behind the left earlobe. Although the data indicate significant improvement in microcirculation in the target area, it remains to be shown that this phenomenon is an indication of changes in the inner ear and that these in turn are responsible for improvements in vertigo in clinical practice. Nevertheless, the current data are highly suggestible of real effects of Vertigoheel and should stimulate further research in this field. Further, as the study was non-randomized, selection bias cannot be entirely excluded, although the consistency of the results is reassuring.

A major overall finding was an improvement in blood flow, measured on several variables. The increase in the number of blood-cell perfused nodal points in the network of microvessels indicates an improvement in the distribution of blood in the microcirculation. This variable is a measure of the dynamic state of the vessel. An increase in the number of nodal points reflects both improved conditions of blood flow (microvessel response) and flow characteristics of the blood (rheological response). However, it cannot be determined from this number alone which of the responses contributes the most to the observed effects. Blood flow increased with Vertigoheel treatment, both in arterioles and venules whereas there was no difference or a slight decrease in the control group. The slight reduction in hematocrit with treatment might also have contributed to the increased flow rate by reducing the viscosity of the blood (Nuttall et al., 1988). The increased vasomotion observed in the Vertigoheel group would also contribute to improvements in local blood flow and indicates effects on vascular smooth muscle from the active therapy. A further sign of increased blood flow were the increases in partial oxygen pressure in the Vertigoheel-treated patients compared with control which indicated an improved catabolic balance in the analyzed microcircular networks.

A greater number of adhering leucocytes were observed with Vertigoheel treatment and this was accompanied by a corresponding increase in the relative concentrations of the adhesion marker ICAM-1. The SPEX system has been used with good reproducibility in other systems (Klopp et al., 2001, 2002) and the results in the current assay were consistent with the other results. Thus, change in mobilization of leucocytes might indicate improvement in membranes and in cellular responses (Goldsmith and Spain, 1984; Smith et al., 1979) as well as a direct effect on the immune system. The contribution of possible immunological effects to the overall benefits from Vertigoheel in the current work must remain an object for speculation, although the differences between the treatment groups were statistically significant. Effects on the immune system from homeopathic and homotoxicologic preparations have been postulated by some researchers (Heine, 1999) and this area would benefit from further research.

It is interesting to note that the differences between treatment effects for most variables started early and increased during the course of the trial. Number of nodal points, vasomotion, the adherence of leucocytes, and concentrations of ICAM cells improved continuously during the treatment period in the Vertigoheel group whereas there was little or no change in the control group. This indicates that the there was no plateau for the effects of Vertigoheel and that no tolerance or resistance to treatment developed over the study period.

The clinical observations, which showed greater improvement in severity of vertigo in the Vertigoheel group but no change or slight worsening of symptoms in the control group, are probably not robust enough to be taken as proof of efficacy. Dizziness is difficult to quantify (Jacobson and Newman, 1990) and there is also a certain degree of spontaneous improvement in vestibular nystagmus, the measurement used in this study to determine severity of vertigo. However, the differences between treatment groups and the accordance between improvements assessed by the physician and evaluated by the patients support the possible clinical benefits. Larger studies of varying design have indicated clinical benefits with Vertigoheel (Claussen et al., 1984; Daroff and Martin, 2001; Wolschner et al., 2001; Issing et al., 2005). The data do not allow us to attempt an assessment of the relative influence of the different variables investigated on clinical outcomes, although such information would be very valuable both for a greater understanding of the specific agent used in the present study and for a further understanding of herbal medicines and homeopathic remedies.

Similarly, the tolerability data are not based on a sufficient sample size to be more than indicative, but they are in accordance with the good tolerability reported previously for Vertigoheel and indeed for homeopathic treatments in general (Claussen et al., 1984; Metzger, 1964; Schröder et al., 2003; Strösser and Weiser, 2000; Weiser et al., 1998; Wolschner et al., 2001; Zenner and Metelmann, 1991). Tolerability is an intermediary aspect between the poles of pharmacological efficacy and the psychological

benefits which probably all contribute to the multifaceted benefits from the alternative medication. The experience of a disruption of the natural equilibrium and the sensation of imbalance and instability associated with vertigo can be a strong psychological burden on patients and the non-pharmacological aspect of therapies may be particularly important in such cases as vertigo. Good tolerability contributes to a positive patient experience with treatments and increases the likelihood of patients staying on therapy (Hansson, 2002).

In summary, we have shown that 12 weeks treatment with a commonly used homeopathic treatment for vertigo, Vertigoheel, leads to significant changes in subcutaneous microcirculation in different target areas. These results indicate a pharmacological effect from the treatment, which needs further study to clarify what active constituents are responsible for the observed effects and by what mechanisms these might be effected.

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