Treatment of Vertebrobasilar Insufficiency–Associated Vertigo with a Fixed Combination of Cinnarizine and Dimenhydrinate

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Abstract: Thirty-seven patients suffering from vertigo associated with vertebrobasilar insufficiency participated in our prospective, single-center, double-blind, comparative study. Patients were randomly allocated to treatment with placebo; betahistine (12 mg betahistine dimesylate, one tablet three times daily); or the fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate (one tablet three times daily) for 4 weeks. The primary efficacy end point was the decrease of the mean vertigo score (S_M), which was based on the patients' assessments of 12 individual vertigo symptoms after 4 weeks of treatment. Patients treated with the fixed combination showed significantly greater reductions of S_M as compared to patients receiving placebo ($p < .001$) or the reference therapy betahistine ($p < .01$). The vestibulospinal parameter lateral sway (Unterberger's test) improved to a significantly greater extent in patients taking the fixed combination as compared to those receiving placebo ($p < .001$). No serious adverse event was reported in any therapy group. The tolerability of the fixed combination was judged as very good or good by 91% (betahistine, 73%; placebo, 82%). In conclusion, the fixed combination proved to be statistically more effective than the common antivertiginous drug betahistine in reducing vertebrobasilar insufficiency–associated vertigo symptoms.

Key Words: betahistine; cinnarizine; dimenhydrinate; vertebrobasilar insufficiency; vertigo

The maintenance of balance is an essential condition for the management of daily activities. This complex physical performance is based on finely tuned brain processing of sensory inputs provided by the vestibular, visual, and proprioceptive systems and the cognitive system. Data mismatch induced by unusual and therefore unadapted stimulation of the intact sensory systems, or pathological dysfunction of any of these afferent components or of the brain centers integrating these signals, leads to vertigo [1,2]. Therefore, vertigo not only represents a cardinal symptom for vestibular disorders, but it can be associated with a wide spectrum of disorders, including internal diseases, or it may be of psychogenic origin [3,4].

The vertebrobasilar system is responsible for the blood supply of 10 cranial nerves, all ascending and descending tracts, parts of the cortical hemispheres, and the end-organs of hearing and balance. Thus, dysfunction of this system can lead to a wide variety of symptoms. Cerebrovascular disease is a common cause of vertigo symptoms, particularly in older patients [5]. Vertigo is one of the first and most frequent signs of vertebrobasilar insufficiency (VBI), with a relative incidence ranging from 50% to 80% [5]. VBI is characterized by transient ischemic attacks, and it represents a heterogeneous disease entity with many potential causes [6–8]. It usually results from atherosclerosis of the subclavian, vertebral, and basilar arteries with insufficient collateral circulation but may also be due to other causes, such as compression of vertebral arteries by cervical spondylosis or

the subclavian steal syndrome [5,7]. VBI presents with characteristic symptoms and signs owing to impaired perfusion of the cerebellum, the brainstem, and the occipital cortex [8]. Its main symptom—vertigo—results from an insufficient blood supply in the vestibulocerebellar complex [9]. Because vestibular pathways are widely distributed in the hindbrain and because the vestibular end-organ is supplied by vertebrobasilar circulation, in VBI the vestibular system may be affected at any level: the labyrinth, the eighth cranial nerve, or the vestibular nuclei [5]. This may explain why vertigo is the most frequent and sometimes the only symptom in VBI [10,11]. Typically, VBI-associated vertigo occurs in attacks, depends on position, and is frequently associated with nystagmus, nausea, vomiting, and severe imbalance [5]. Concomitant symptoms include blurred vision, blackouts, drop attacks, or headache.

A major concern of drug therapy in VBI is to improve impaired circulation and to restore normal perfusion of compromised areas [6]. Anticoagulant and antiplatelet therapies may serve to reduce the incidence of stroke after transient ischemic attacks [12]. Calcium antagonists are a useful alternative, especially in cases of atherosclerotic origin [13]. Also, symptomatic treatment is important to provide immediate relief to affected patients. For this purpose, drugs of various pharmacological classes have been used. These include antihistamines (e.g., dimenhydrinate); anticholinergics (e.g., scopolamine); certain calcium channel blockers (cinnarizine, flunarizine); histamine analogs (betahistine); and also diuretics, neuroleptics, and other psychotherapeutic agents; corticosteroids; and hemorheologics [14]. For the treatment of VBI-associated symptoms, including vertigo, betahistine has been described as useful [15].

Here we report on the efficacy and tolerability of a fixed combination consisting of the calcium channel blocker cinnarizine (20 mg) and the antihistamine dimenhydrinate (40 mg). This fixed combination has been used successfully in Germany for 25 years for the treatment of peripheral, central, or combined types of vertigo. The rationale for using the combination is derived from the modes of action of its constituents: Owing to its calcium antagonistic properties, cinnarizine regulates calcium influx into vestibular cells of the labyrinth and improves cerebral circulation [16–18], whereas dimenhydrinate mainly exerts a regulatory effect on the vestibular nuclei and adjacent vegetative centers in the brainstem [19,20].

The antivertiginous efficacy of the combination was demonstrated in a series of open studies [21–24] and in numerous controlled, double-blind, randomized clinical studies that included patients suffering from vertigo of central, peripheral, or combined central-peripheral origin. The results of these studies provided evidence for a syn-

ergistic effect of cinnarizine and dimenhydrinate at doses reduced by up to two and a half times as compared to the doses commonly used in monotherapy [25–30]. Our double-blind, randomized clinical study focused on vertigo caused by VBI. Episodic, intense vertigo frequently represents the first and, in combination with neurosensory signs of brainstem dysfunction, the most important symptom in VBI [31]. Vertigo is most frequently associated with vision disturbances, patients often report nausea and vegetative symptoms, and perhaps one-third of the patients complain about severe headaches [3]. In view of the pharmacological properties of the active substances in the fixed combination—in particular the cerebral selectivity of the calcium antagonist cinnarizine and the brainstem-regulating properties of dimenhydrinate—and encouraged by the positive results obtained in a previous open study [21], we performed this trial to investigate the antivertiginous effects of the fixed combination in VBI as compared to the effects of betahistine dimesylate. To quantify possible nonspecific effects during treatment, we included a placebo group.

SUBJECTS AND METHODS

Patient Population

Eligible participants were men and women who suffered from VBI and, in addition to the cardinal symptom vertigo, showed at least two of the following symptoms: impaired hearing, impaired vision, tinnitus, or headache. Diagnosis of VBI had to be confirmed by the presence of typical abnormalities in specific examination tests. We excluded from participation patients who suffered from vertigo due to diseases other than VBI (e.g., cardiovascular diseases). Pregnant or lactating women or women without safe contraception during the study were also excluded. Other exclusion criteria were gastrointestinal ulcers, bronchial asthma, adrenal tumors, angle-closure glaucoma, prostate adenoma with residual urine, suspicion of compressive intracranial processes, Parkinson's disease, pheochromocytoma, alcohol abuse, acute intoxication, and convulsive disorders. Further exclusion criteria were the concomitant use of monoamine oxidase inhibitors or aminoglycoside antibiotics. Previous antivertiginous medication had to be discontinued in a 2-week washout phase prior to the start of treatment.

Study Design and Treatment

We designed the study as a randomized, double-blind, reference- and placebo-controlled, single-center, phase III clinical study with three parallel groups. It was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki (1989 revision). The ethics committee at the Otto-von-Guericke Univer-

sity, formerly the Medical Academy, Magdeburg, reviewed and approved the study documents. All patients received oral and written information about the study and provided written informed consent before enrollment. We randomly assigned enrolled patients to 4 weeks of treatment with either the fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate (one tablet three times daily) or the reference medication betahistine (12 mg betahistine dimesylate per tablet, one tablet three times daily) or placebo (one tablet three times daily). Randomization was based on a computer-generated block sequence that ensured equal distribution of patients among the treatment groups, according to Food and Drug Administration standards. The study medications were manufactured by Hennig Arzneimittel in accordance with good manufacturing practice. To guarantee double-blind conditions, test medication, reference medication, and placebo were indistinguishable with respect to appearance, taste, weight, shape, and packaging.

Efficacy Measures

Patients were subjected to an entry examination (first visit, before start of treatment), an intermediate examination (second visit, after 7 ± 2 days), and a final examination (third visit, after 28 ± 2 days). On the occasion of each visit, patients underwent an efficacy evaluation that was based primarily on the patients' assessments of the intensities of their vertigo symptoms. As the primary efficacy end point, the change of the mean vertigo score (S_M) after 4 weeks was used as a parameter for vertigo intensity. S_M was defined as the mean of the intensities of six vertigo symptoms and vertigo as a consequence of six trigger factors, as evaluated by the patients. The assessed symptoms at each visit were unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, swaying, and vertigo due to change of position, bowing, getting up, walking, head movements, and eye movements. Patients evaluated their vertigo symptom intensities on the basis of a standardized questionnaire using a graded 4-point visual analog scale ranging from 0 (no symptoms) to 3 (strong symptoms). Treatment efficacy was analyzed by comparing S_M changes from baseline resulting from either medication. Secondary variables of efficacy were additional VBI symptoms (see later), vegetative symptoms, and vestibulospinal, vestibuloocular, and audiometric variables. In addition, the overall efficacy of the treatment was rated by both patients and investigator after 4 weeks on a 5-point verbal rating scale: *very much improved*, *much improved*, *slightly improved*, *not improved,* or *deteriorated*.

The VBI symptoms—headache, tinnitus, impaired hearing, impaired vision, aural fullness, ocular muscle pareses, and bulbar symptoms—were rated by the pa-

tients. In addition, the patients were asked about the intensities of vegetative symptoms that are often associated with vertigo. For evaluation purposes, the scores for the symptoms of nausea, vomiting, sweating, and tachycardia were integrated to a mean vegetative score (V_M), which was analyzed in the same way as was S_M.

We performed Unterberger's and Romberg's tests and registered the results by craniocorpography (CCG), as described elsewhere [3]. Briefly, CCG is a diagnostic procedure by which characteristic light patterns corresponding to the head-body sway of an affected patient are recorded. From these patterns, we determined deviation of the patient to the right or to the left (angular deviation), body spin, staggering of the patient's head and body (lateral sway), and longitudinal deviation using Unterberger's test, and anteroposterior shift and lateral shift using Romberg's test.

We analyzed spontaneous and positional nystagmus using Frenzel's glasses. Gaze nystagmus was examined under the following conditions: glance to the right, to the left, straight ahead, and upward. We determined positional nystagmus by monitoring the eyes for nystagmus in the following positions: supine with head downward, sitting up, and dorsal with head to the right and to the left, respectively.

We performed the bithermal caloric test using electronystagmography. Nystagmus was induced by irrigation of the external auditory canal of the left and the right ear with 20 ml water at either 30° or 44°C. Computer-assisted evaluation involved the following parameters: nystagmus frequency (beats/30 sec), amplitude (deg), cumulation time (s), total amplitude (deg), and slow-phase velocity (deg/sec).

For an objective assessment of hearing function, we performed audiometric tests according to standard procedures using pure tones, words, and numbers as criteria for assessment of hearing loss. We performed pure-tone threshold audiometry at increasing frequencies, considering the left and right ears separately. In addition, speech audiometry served to evaluate hearing loss for words and numbers and of speech discrimination capacity. All tests were performed according to standard procedures. Auditory brainstem responses were evaluated by means of brainstem evoked response audiometry.

Tolerability

Tolerability assessment was based on reports of adverse events that occurred after drug intake. The events were reported spontaneously by the patients, observed by the investigator, or reported by the patients in response to general questioning by the investigator. Adverse reactions were registered in detail at each visit. At the end of the final visit, patients and the investigator rated the overall

tolerability using a 4-point verbal rating scale: *very good, good, moderate,* or *poor*.

Statistical Analysis

Confirmatory analysis of the primary efficacy variable S_M was based on its change from baseline in hierarchical order: (first) 4 weeks after start of treatment and (second) 1 week after start of treatment. We analyzed differences between the test medications by a one-tailed Student's *t* test in the case of sufficient normal approximation of the initial distribution at a global significance level $\alpha = 0.05$. In cases of insufficient normal approximation, a non-parametric Kruskal-Wallis test was used at a global significance level of $\alpha = 0.05$. An analysis of covariance was performed with adjustment of means at the end of the study, using the initial values as covariate in cases of insufficient homogeneity of the initial distributions. We performed homogeneity tests at the 20% level for the primary variable under consideration and for the parameters of age, gender, the Broca index, and body mass index. Confirmatory efficacy analysis was based on the

changes in S_M during therapy as determined for the collective of patients completing the study according to protocol (per-protocol analysis). The intent-to-treat collective was defined as those patients for whom the primary efficacy variable was at least determined at the entry and at one further examination. A separate intent-to-treat analysis was not performed because the two patient collectives were identical. All statistical tests carried out on secondary variables were strictly interpreted in an exploratory manner. For analysis of the changes from baseline within a treatment group in the course of the study, we used the Wilcoxon signed rank test. Frequency distributions were analyzed by means of Fisher's exact test.

RESULTS

Disposition of Patients and Demographic Characteristics

Thirty-seven white outpatients were enrolled in the study to receive either the fixed combination (n = 11), betahistine (n = 13), or placebo (n = 13). Table 1 shows

Table 1. Selected Demographic and Anamnestic Data

	Fixed Combination (n = 11)	Betahistine (n = 13)	Placebo (n = 13)
Male/female (no. of patients)	2/9	6/7	1/12
Age (yr)			
Mean ± SD	52.64 ± 9.45	51.92 ± 10.28	49.54 ± 12.11
Range	39–64	35–70	31–64
Weight (kg)			
Mean ± SD	71.18 ± 9.94	75.15 ± 15.43	71.38 ± 10.64
Range	55.00–92.00	52.00–110.00	52.00–90.00
Height (cm)			
Mean ± SD	165.73 ± 8.34	169.00 ± 7.52	164.77 ± 9.42
Range	155.00–178.00	158.00–185.00	150.00–186.00
Body mass index (kg/m^2)[a]			
Mean ± SD	25.87 ± 2.69	26.19 ± 4.53	26.45 ± 4.48
Range	22.89–32.21	20.57–38.06	19.10–36.05
Duration of illness (mo)			
Mean ± SD	55.40 ± 56.50	41.19 ± 53.33	42.92 ± 20.32
Range	1.00–168.00	3.50–192.00	18.00–96.00
Patients with premedication			
Number	4	6	5
Percentage per group	36.36	46.15	38.46
Patients with concomitant diseases[b]			
Number	7	6	5
Percentage per group	63.64	46.15	38.46
Patients with concomitant medication			
Number	5	7	4
Percentage per group	45.45	53.85	30.77

SD = standard deviation.
[a]Body mass index = body weight in kilograms/(height in meters)^2.
[b]Also includes patients reporting previous diseases and operations.

the demographic and other baseline attributes of all patients. The three therapy groups were comparable with respect to demographic variables and medical history. The duration of illness before enrollment in the study varied between 1 month and 16 years, with overall means in the therapy groups of 3.4–4.6 years. Approximately 40% of the patients in each group were on drug therapy at the time of study onset (premedication), and some of them received more than one medication at a time. The most frequently administered active substance was betahistine dimesylate, which had been taken by one patient of the betahistine group, three patients of the fixed-combination group, and two patients of the placebo group. Of the study patients, three (i.e., two in the betahistine group and one in the placebo group) had received the combination of cinnarizine and dimenhydrinate as premedication. All patients admitted to the study suffered from diagnostically established VBI. Two patients each in the betahistine and placebo groups terminated the study prematurely between the entry and the follow-up examinations. Three of the four dropouts discontinued the study owing to unknown reasons. The fourth patient (betahistine group) could not continue the study because of an internal disease. All 33 patients who completed the study (11 per treatment group) fulfilled the criteria for per-protocol analysis and were included in the efficacy analysis. Treatment compliance was confirmed by questioning the patients and by an investigator's checking of empty blister strips at the end of the study.

Clinical Efficacy

Vertigo Symptoms

The primary efficacy variable was the reduction of the mean vertigo score (S_M) in the course of the 4-week therapy. Comparison between the therapy groups (the Kruskal-
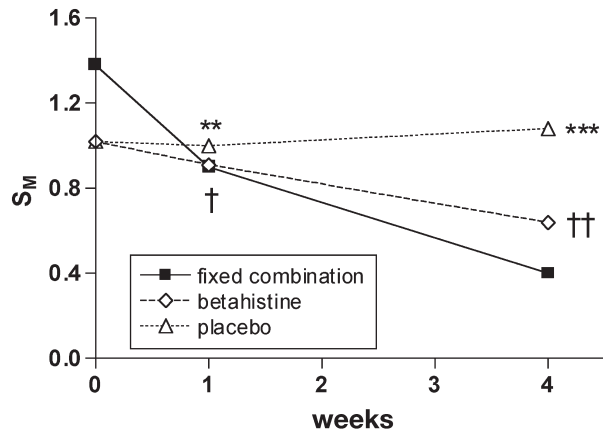

Figure 1. Change of the mean vertigo score, S_M (primary efficacy variable), in the course of the study. S_M was defined as the mean of the patients' judgments of six vertigo symptoms and vertigo in consequence of six factors giving rise to vertigo (see Efficacy Measures). Fixed combination vs. placebo, ***$p <$ .001, **$p <$ .01. Fixed combination vs. betahistine, ††$p <$ .01, †$p <$ .05 (exceeding probability of Kruskal-Wallis statistics, adjusted by ANCOVA).

Wallis test) showed an imbalance in initial distribution at the 20% significance level. Thus, initial S_M baseline scores in the fixed-combination group were higher than those in the betahistine ($p =$ .044) and placebo ($p =$ .093) groups. Significantly greater reductions of S_M found in the fixed-combination group became evident 1 week after the start of treatment (vs. betahistine, $p <$ .05; vs. placebo, $p <$ .01). During 4 weeks of therapy, the fixed combination decreased S_M some 2.5-fold as compared to betahistine ($p <$ .01). In the placebo group, S_M scores remained largely unchanged in the course of therapy (fixed combination vs. placebo after 4 weeks, $p <$ .001). Changes in S_M during the 4-week double-blind treatment period are summarized in Table 2 and Figure 1.

Table 2. Changes of the Mean Vertigo Score (S_M) After 1 and 4 Weeks

	After 1 Week		After 4 Weeks	
	Mean Change	**p Value**[a]	**Mean Change**	**p Value**[a]
Fixed combination				
Mean change ± SD	−0.48 ± 0.38[c]	—	−0.98 ± 0.42[c]	—
Adjusted mean[b]	−0.68	—	−1.15	—
Betahistine				
Mean change ± SD	−0.11 ± 0.29	.014	−0.38 ± 0.45[d]	.005
Adjusted mean[b]	−0.01	.037	−0.30	.007
Placebo				
Mean change ± SD	−0.02 ± 0.24	.002	+ 0.07 ± 0.22	<.001
Adjusted mean[b]	+0.08	.008	+ 0.15	<.001

SD = standard deviation.
[a]Exceeding probability vs. fixed combination, Kruskal-Wallis test.
[b]Calculated after adjustment for nonhomogeneous initial distribution by analysis of covariance.
[c]$p <$ .01, exceeding probability of Wilcoxon signed rank test for changes from baseline within each therapy group.
[d]$p <$ .05, exceeding probability of Wilcoxon signed rank test for changes from baseline within each therapy group.

Table 3. Headache Before and After 4 Weeks of Therapy

	No. of Patients with Headache Before Treatment/After 4 Weeks			
	Fixed Combination (n = 11)	Betahistine (n = 11)	Placebo (n = 11)	Total (n = 33)
Headache present	10/8	11/9	11/11	32/28
Localization				
Diffuse	9/6	11/8	10/10	30/24
Punctiform	0/0	0/0	1/1	1/1
One-sided	0/0	2/1	3/3	5/4
Frontal*	5/1	4/3	8/9	17/13
Occipital	10/7	11/9	11/11	32/27
Type (character)				
Attacks	10/8	9/8	10/9	29/25
Continuous	4/0	2/1	4/4	10/5
Paroxysmal	1/0	2/0	0/0	3/0

*p = .002, exceeding probability of Fisher's exact test for the comparison of frequency distribution after 4 weeks.

Further Symptoms of VBI

At the start of the study, all patients except one in the fixed-combination group complained about headache. The three therapy groups were homogeneous with respect to initial distribution of headache as evaluated according to localization and type. Descriptive analysis of the effects of the therapy is based on the number of patients still reporting headache after 4 weeks of therapy (Table 3). The symptom had subsided completely in two patients in each of the fixed-combination and betahistine groups by the end of the treatment but was still present in all patients treated with placebo.

Analogous to the vertigo symptoms, the evaluation of further VBI symptoms was based on the subjective judgment of intensity (i.e., mean scores). Initially, all further symptoms were homogeneously distributed among the therapy groups, except for higher mean scores of tinnitus and impaired hearing in the placebo group (Table 4). Considering the entire study population, the most prominent additional symptom was tinnitus, with an initial mean score of 1.55 ± 0.83 (N = 33). In the fixed-combination group, tinnitus progressively diminished in the course of therapy, with a significant decrease after 4 weeks (p = .016, Wilcoxon signed rank test with respect to baseline). Mean scores for tinnitus showed a moderate, insignificant decrease under betahistine (p = .125) but remained nearly unaffected under placebo (see Table 4). The change in the mean score for tinnitus observed after 4 weeks of therapy with the fixed combination (-0.73 ± 0.65) was more pronounced than that in the betahistine group (-0.45 ± 0.69). The differences were, however, not statistically significant. Of the other symptoms evaluated, bulbar symptoms and impaired vision were the next most prominent, followed by impaired hearing and aural fullness. Again, all the symptoms showed an improvement under the fixed-combination therapy, with decreases in mean scores of more than 50% after 4 weeks. The patients treated with betahistine showed minor im-

Table 4. Further Vertebrobasilar Insufficiency Symptoms Before and After 4 Weeks of Therapy

	Mean Score ± SD			
	Fixed Combination (n = 11)	Betahistine (n = 11)	Placebo (n = 11)	Total (n = 33)
Tinnitus				
Initial score	1.18 ± 0.75	1.36 ± 0.67	2.09 ± 0.83[a]	1.55 ± 0.83
Score after 4 weeks of therapy	0.45 ± 0.52	0.91 ± 0.83	1.91 ± 0.83[d]	
Impaired hearing				
Initial score	0.45 ± 0.69	0.55 ± 0.52	1.18 ± 0.87[a]	0.73 ± 0.76
Score after 4 weeks of therapy	0.18 ± 0.40	0.64 ± 0.67	1.18 ± 0.87[c]	
Impaired vision				
Initial score	1.18 ± 0.87	1.00 ± 0.77	1.00 ± 0.77	1.06 ± 0.79
Score after 4 weeks of therapy	0.45 ± 0.52	0.64 ± 0.67	1.18 ± 0.75[b]	
Aural fullness				
Initial score	0.55 ± 0.69	0.45 ± 0.52	0.64 ± 0.81	0.55 ± 0.67
Score after 4 weeks of therapy	0.09 ± 0.30	0.27 ± 0.65	0.55 ± 0.82	
Bulbar symptoms				
Initial score	1.18 ± 0.75	1.27 ± 0.90	1.27 ± 1.01	1.24 ± 0.87
Score after 4 weeks of therapy	0.55 ± 0.69	0.82 ± 0.75	1.09 ± 0.94	

SD = standard deviation.
[a]Nonhomogeneous distribution at the 20% significance level, Kruskal-Wallis test.
[b]$p < .05$ vs. fixed combination, Kruskal-Wallis test.
[c]$p < .01$ vs. fixed combination, Kruskal-Wallis test.
[d]$p < .001$ vs. fixed combination, Kruskal-Wallis test.

provements, and almost no change occurred during therapy in the placebo group (see Table 4).

Vegetative Symptoms

Before the start of therapy, distribution of V_M was homogeneous, with mean values of 0.55–0.77 in the therapy groups (Fig. 2). As in the case of vertigo symptoms, the vegetative symptoms were reduced more effectively by the fixed combination than by the comparators. After the 4-week combination therapy, V_M reached a score of 0.16 ± 0.23, which corresponds to a reduction by more than 80% of initial scores ($p = .004$, Wilcoxon signed rank test with respect to baseline; Table 5). In patients in the betahistine group, V_M showed a minor, insignificant decrease (approximately 30%) within the first week but no further improvement until the end of the study. Despite the superiority of the fixed combination, the comparison with betahistine was found not to be statistically significant ($p = .052$, Kruskal-Wallis test). In the placebo group, V_M scores remained largely constant (see Table 5). Statistical analysis showed a significant superiority of the fixed combination versus placebo after 4 weeks of therapy ($p = .019$).

Craniocorpography

The results of the parameter lateral sway in Unterberger's and Romberg's tests are shown in Table 6. Statistical analysis of the initial distribution of all parameters derived from CCG indicated comparability of the therapy groups. Only patients in the placebo group initially showed slightly lower values for lateral sway (Unterberger's test) as compared to the fixed-combination group ($p = .130$). Lateral sway in both tests progres-
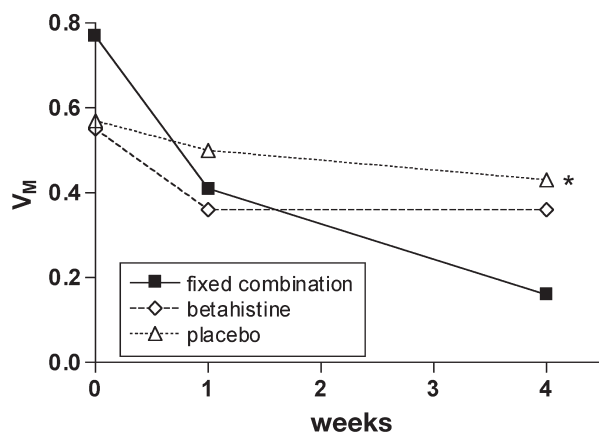

Figure 2. Change of the mean vegetative symptom score, V_M, in the course of the study. The patients judged the intensity of the four symptoms of nausea, vomiting, sweating, and tachycardia (see Efficacy Measures). Fixed combination vs. placebo, *$p < .05$ (exceeding probability of Kruskal-Wallis statistics).

Table 5. Changes of the Mean Vegetative Score (V_M) After 1 and 4 Weeks

	After 1 Week		After 4 Weeks	
	Mean Change ± SD	**p Value[a]**	**Mean Change ± SD**	**p Value[a]**
Fixed combination	−0.36 ± 0.66		−0.61 ± 0.60[b]	
Betahistine	−0.18 ± 0.25	.945	−0.18 ± 0.34	.052
Placebo	−0.07 ± 0.20	.331	−0.14 ± 0.26	.019

SD = standard deviation.
[a]Exceeding probability vs. fixed combination, Kruskal-Wallis test.
[b]$p < .01$, exceeding probability of Wilcoxon signed rank test for changes from baseline within each therapy group.

sively decreased in the course of the active treatments, more markedly under the fixed combination than under betahistine. As to the lateral sway in Unterberger's test, the changes from baseline in the fixed-combination group were significant after 1 week ($p < .05$) and after 4 weeks ($p < .001$; see Table 6). At the end of therapy, the lateral sway in the two tests showed mean decreases of some 50–60% in patients in the fixed-combination group as opposed to a reduction of 25–40% in those in the betahistine group. A significant superiority of the combination versus placebo was found in both the Unterberger's ($p < .001$) and Romberg's tests ($p < .05$), whereas differences versus betahistine were not significant (see Table 6).

Nystagmus Tests

Evaluation by Frenzel's glasses showed no clear evidence for spontaneous nystagmus in any patient either initially or in the course of the study. More than one-half of the patients in each therapy group initially showed a positional nystagmus in at least one position. The number of patients with positional nystagmus decreased insignificantly in the course of therapy with betahistine and the fixed combination but increased under placebo (not shown).

Also, no significant difference was seen between patients in the three treatment groups with respect to the caloric test variables, either at baseline or in the course of the study.

Audiometry

Both in pure-tone and the speech audiometry, the proportion of patients presenting hearing loss remained unaffected in the course of therapy with any of the study medications. As to brainstem evoked response audiometry, no significant difference was noted between the therapy groups, either at baseline or in the course of therapy (not shown).

Table 6.　Craniocorpography: Lateral Sway (Unterberger's and Romberg's Test) in the Course of Therapy

	Lateral Sway (cm)		
	Fixed Combination (n = 11) Mean ± SD	**Betahistine (n = 11) Mean ± SD**	**Placebo (n = 11) Mean ± SD**
Unterberger's test			
Before therapy	17.48 ± 4.86	16.85 ± 6.62	14.03 ± 6.45[a]
Change after 1 week	−5.17 ± 4.43[b]	−6.22 ± 8.32[b]	−1.15 ± 4.56
(*p* value vs. fixed combination)	—	(0.622)	(0.034)
Change after 4 weeks	−10.23 ± 4.89[c]	−6.47 ± 7.44[b]	+1.79 ± 4.79
(*p* value vs. fixed combination)	—	(0.277)	(<0.001)
Romberg's test			
Before start of therapy	8.50 ± 8.75	6.36 ± 2.16	5.64 ± 2.66
Change after 1 week	−2.05 ± 5.97	−2.00 ± 2.37[b]	−0.36 ± 6.05
(*p*-value vs. fixed combination)	—	(0.364)	(0.894)
Change after 4 weeks	−4.27 ± 8.20	−1.45 ± 2.98	+0.82 ± 2.56
(*p*-value vs. fixed combination)	—	(0.595)	(0.038)

SD = standard deviation.
[a]Nonhomogeneous distribution at the 20% significance level, Kruskal-Wallis test.
[b]$p < .05$, exceeding probability of Wilcoxon signed rank test for changes from baseline within each therapy group.
[c]$p = .001$, exceeding probability of Wilcoxon signed rank test for changes from baseline within each therapy group.

Investigator's and Patients' Assessment of Efficacy

The assessments by investigator and patients were similar and coincided with the decrease in vertigo symptoms observed under therapy with the fixed combination. Accordingly, approximately 73% of the patients in the fixed-combination group, but only 36% of patients in the betahistine group, assessed their health condition as much improved or very much improved at the end of the study. The ratings of slightly improved and not improved were each given by one patient in the fixed-combination group, whereas no patients in this group considered their health condition to be deteriorated. In contrast, approximately one-half of the patients treated with betahistine stated a slight improvement, and two patients judged the efficacy with the ratings of not improved and deteriorated. The judgments in the placebo group reflected the lack of efficacy of the treatment, with the rating of not improved given by eight patients and a rating of deteriorated given by three. Statistical comparison showed a significant difference between the treatments in terms of judgments by both patient and investigator ($p < .001$, fixed combination vs. betahistine and placebo, respectively).

Tolerability

A total of 7 of the 37 randomly assigned patients reported adverse events (AEs) in the course of the study. The rate of AEs was 18.2% in patients in the fixed-combination group (two patients, five AEs) and 38.5% in those in the betahistine group (five patients, nine AEs). No AE was reported in the placebo group. As to the reports from the betahistine group, all AEs except one (vertigo) involved gastrointestinal system disturbances that represent known adverse drug reactions to this substance. Of the two patients reporting AEs in the fixed-combination group, one reported symptoms of an upset gastrointestinal tract (not likely to have been related to medication intake, in the opinion of the investigator, as the symptoms subsided after 2 days without interruption of treatment). The second patient in this group reported an AE involving a strong response to the caloric test. In the investigator's view, this was not related to study medication. No AE led to premature discontinuation of the study, and no serious or unexpected AE was encountered during the study.

The investigator rated the tolerability of the study medication as good in all patients except for one patient in the betahistine group, for whom the tolerability was judged as moderate. Regarding the patients' judgments, statistical calculation showed a significant difference between the treatments ($p = .019$, Fisher's exact test), with the fixed combination showing the best ratings. All patients in this group (except for one missing value) judged the tolerability of the medication as very good or good (five patients per rating; 90.9%). In the comparator groups, the rating of very good was given only once (betahistine group). The vast majority of the patients receiving betahistine (63.6%) or placebo (81.8%) rated the tolerability as good. Furthermore, three patients in the betahistine group (27.3%) judged the tolerability as moderate. In the placebo group, the ratings of moderate and poor were each given once.

DISCUSSION

Evaluating therapy success in patients suffering from vertigo is often difficult owing to the complexity of this disease and the lack of unambiguous apparatus-based parameters. Primarily, the crucial criterion for evaluating therapy success is the subjective severity of vertigo symptoms tormenting the patient. The reduction of symptom intensity is the most direct and important parameter for the evaluation of a patient's vertigo complaints in the course of an antivertigo treatment. Nevertheless, apparatus-based methods are useful to corroborate the results of the vertigo diagnosis. In addition to thorough evaluation of case history, such tools are helpful for establishing the correct diagnosis for the individual patient. In our study, both subjective symptom-based and apparatus-based measures were used to measure therapy success. Because S_M represents a parameter for the evaluation of vertigo severity and characterizes the intensity of an individual patient's vertigo sensations independently of the type of vertigo, it serves as a well-established and effective measure of therapeutic progress [25–30].

The efficacy of the fixed combination and its superiority over betahistine can be explained by the pharmacodynamic properties of the two medications. The antivertiginous effect of betahistine is considered to rely mainly on improvement of microcirculation in the inner ear [32,33]. Also, an interaction with H_3-receptors has been suggested [34]. There is some evidence for an inhibitory activity of betahistine on polysynaptic type-I neurons in the lateral vestibular nuclei [35]. As a result of these effects, betahistine leads to a reduction of vertigo symptoms, and it is therapeutically useful particularly for the treatment of peripheral vestibular disorders and especially Ménière's disease [36]. The combination, on the other hand, shows a dual mechanism of action acting both peripherally and centrally. The calcium antagonist cinnarizine, similarly to betahistine, acts by enhancing circulation in the peripheral vestibular organ and in compromised intra- and extracranial areas [16, 17]. Recently it was shown that cinnarizine directly affects calcium ion flux at calcium channels of vestibular outer hair cells [37,38]. The beneficial effects of this substance class in VBI have been demonstrated both experimentally and clinically [39,40]. The antivertiginous efficacy of cinnarizine in patients with cerebrovascular disorders [14] is considered to rely on an increase in blood flow to the vestibular nuclei, which in turn results in improved neuronal responsiveness of polysynaptic neurons [41]. In the combination, the actions of cinnarizine are reinforced by those of dimenhydrinate. By means of dampening the entire medial longitudinal bundle, dimenhydrinate inhibits the spreading of impulses at the medullar vestibular nuclei [19] that are closely associated with the vegetative regulatory centers [20]. The vertigo symptoms and the concomitant vegetative complaints, particularly nausea and vomiting, are thereby reduced. The trigger zone at the base of the fourth ventricle in the brainstem is inhibited as well [20]. On the basis of these joined actions, the combination exerts a rapid and effective antivertiginous effect. The two active substances complement each other synergistically [25]. Hence, the fixed combination not only effectively reduced the vertigo symptoms but decreased the concomitant vegetative symptoms to a statistically significant degree as compared to placebo. Particularly the distressing symptoms of nausea, vomiting, and tachycardia had ceased after the 4 weeks of fixed-combination therapy. Also, the scores of the concomitant VBI symptoms of tinnitus, impaired hearing, and impaired vision decreased significantly under the fixed-combination therapy as compared to placebo.

The present results have proven that the fixed combination of cinnarizine and dimenhydrinate is an effective treatment option in treating vertigo due to VBI. These findings are consistent with those from previous studies, which demonstrated a high antivertiginous efficacy of the fixed combination in the treatment of patients suffering from vertigo of peripheral vestibular, central vestibular or—very common in medical practice—combined peripheral-central vestibular origin and Ménière's disease. In these randomized, double-blind, placebo-controlled or reference-controlled clinical studies, the efficacy and tolerability of the fixed combination was superior to various standard treatments, including betahistine [25–30]. Thus, as a superior efficacy of the fixed combination in treating vertigo of various origins has been repeatedly shown, the present results further underscore the broad efficacy of the antivertiginous fixed combination. Its dual central and peripheral mode of action represents a distinct advantage for its therapeutic use, leading to high responder rates. In addition to a higher efficacy, the fixed combination also showed a more favorable safety profile than betahistine. All patients treated with the combination judged the tolerability as good or very good. Despite the absence of AEs, the tolerability judgments in the placebo group were more negative, which probably resulted from the lack of efficacy in patients receiving placebo.

Owing to organizational and technical changes at the ear, nose, and throat clinic of the Otto-von-Guericke University, formerly the Medical Academy, Magdeburg, at the time of the study, the investigations had to be terminated prematurely. By that time point, 37 patients had completed the study instead of 60, as initially planned. From the observed results, it seems likely that the superiority of the fixed combination compared to betahistine would have been even more pronounced had the initially intended number of patients been investigated.

In conclusion, the fixed combination containing 20 mg cinnarizine and 40 mg dimenhydrinate proved to be a safe and effective antivertiginous medication in the treatment of patients suffering from vertigo due to VBI. It showed a favorable benefit-risk ratio and a therapeutic success rate that significantly exceeded that of betahistine.

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