Treatment of Vertigo Due to Acute Unilateral Vestibular Loss with a Fixed Combination of Cinnarizine and Dimenhydrinate: A Double-Blind, Randomized, Parallel-Group Clinical Study

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ABSTRACT

Background: Acute unilateral vestibular loss is a balance disorder that is accompanied by vertigo symptoms and concomitant vegetative symptoms, including nausea and vomiting. Patients are frequently confined to bed rest but may continue to experience vertigo symptoms. A well-established antivertiginous therapy consisting of cinnarizine and dimenhydrinate at low doses may offer rapid relief of acute vertigo symptoms due to acute vestibular loss, without inhibiting physiological compensation processes.

Objective: The purpose of this study was to compare the clinical efficacy and tolerability of a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg versus monotherapy with its respective components in the treatment of acute vertigo symptoms due to acute unilateral vestibular loss.

Methods: In this prospective, single-center, randomized, double-blind, parallel-group clinical study, 50 patients with acute vestibular vertigo were randomly assigned to receive 4 weeks of treatment (1 tablet 3 times daily) with a fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate, 20 mg cinnarizine alone, or 40 mg dimenhydrinate alone. All patients received a 15% mannitol infusion as standard therapy during the first 6 days of treatment. Efficacy was determined by the patients' assessments of vertigo symptoms after 1 and 4 weeks of treatment using a verbal rating scale (vertigo score) and by vestibulo-ocular and vestibulospinal tests. The primary efficacy criterion was defined as the relief of vertigo symptoms after 1 week of treatment.

Results: After 1 week of treatment, the fixed combination was significantly more effective than 20 mg cinnarizine ($P < 0.001$) and 40 mg dimenhydrinate ($P < 0.01$). After 4 weeks, the fixed combination was still significantly more effective than cinnarizine in reducing vertigo symptoms ($P < 0.01$) and significantly more effective than dimenhydrinate in improving the patients' balance while standing ($P < 0.05$). The tolerability of the fixed combination was rated good or very good by 100% of the patients (cinnarizine alone, 82.4%; dimenhydrinate alone, 94.4%). No serious adverse events occurred. Four patients in the fixed combination and the cinnarizine groups, and 6 patients in the dimenhydrinate group reported nonserious adverse events.

Conclusions: The results of this study suggest a distinct benefit in using a fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg versus the respective monotherapies in this population of patients with acute vestibular vertigo. (*Clin Ther.* 2004;26:866–877) Copyright © 2004 Excerpta Medica, Inc.

Key words: vertigo, nystagmus, cinnarizine, dimenhydrinate, combination.

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INTRODUCTION

The maintenance of balance in humans requires an active sensorimotor control system for keeping the body inside its limits of stability.[1] This complex physical task is based on finely tuned brain processing of sensory inputs provided by the vestibular, visual, and proprioceptive systems as well as 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 may lead to the symptom of vertigo.[2,3] Many diseases, such as coronary heart disease, hypertension, or diabetes may be involved in the pathogenesis of unsystematic balance disorders; however, systematic vertigo is caused by disorders of the vestibular system.[4]

Chronic vertigo is more common than vertigo caused by acute vestibular loss. Yet, acute unilateral vestibular loss can have considerable impact,[1,5] because it immediately leads to rotatory vertigo attacks accompanied by spontaneous horizontal-rotatory nystagmus, postural imbalance, nausea, vomiting, and other vegetative symptoms.[2] In addition, sensorineural hearing loss, tinnitus, and aural fullness may occur. Patients presenting with acute vestibular failure are confined to bed rest for up to 1 week.[2] Symptoms caused by acute unilateral vestibular loss are progressively compensated by physiologic adaptation of the brain to the modified situation.[5]

In general, the long-term prognosis is good with respect to patients' ability to manage their daily activities. However, activity restrictions for the patient may persist, and chronification of vertigo symptoms may occur, especially in elderly patients.[6] The prevalence of acute as well as chronified vertigo increases with age, and imposes great limitations on a patient's activities of daily living.[7,8] Patients with vertigo are prone to frequent falls with corresponding injuries.[9] Patients' insecurity while standing and loss of self-confidence as a result of vertigo may further lead to their chronic immobilization. The social consequences of vertigo, together with the increasing age of the population, underscore the importance of developing effective antivertiginous therapies for both individual care and pharmacoeconomic reasons.[10]

Due to the complexity and diversity of the pathogenic mechanisms underlying vertigo, pharmacologic as well as physical therapy approaches have been used in its treatment. Drugs used in the treatment of vertigo include antihistamines, calcium antagonists, histamine analogs (eg, betahistine derivatives), diuretics, neuroleptics and other psychotherapeutic drugs, corticosteroids, and hemorheologic agents.[11] Two commonly used agents are cinnarizine, a selective calcium-channel blocker, and dimenhydrinate, an H_1 antihistamine; these agents have been used successfully for many years in the treatment of vertigo.[11] Cinnarizine acts as an inhibitor of vestibular excitability by suppressing calcium influx into vestibular sensory cells. Through its specific inhibition of calcium entry into arterial smooth muscle cells, cinnarizine improves cerebral and cochlear perfusion.[12–14] Dimenhydrinate exerts antivertiginous and antiemetic effects via its regulatory potential, affecting the vestibular nuclei and closely associated vegetative centers in the brainstem.[15,16]

For more than 20 years, a fixed combination of these 2 drugs has been successfully used for the treatment of vertigo of peripheral, central, or combined peripheral/central origin. The rationale for creating a fixed, low-dose combination of the 2 drugs is based on the dual mode of action of the individual components. Since its introduction in the market, a total of 17 controlled clinical studies have been conducted on the cinnarizine-dimenhydrinate combination. The proven efficacy and good tolerability of the fixed combination versus various standard therapies in the treatment of chronified vertigo have been well established in 7 randomized, double-blind, placebo- and/or reference-controlled clinical studies of patients with various types of vertigo.[17–19] To our knowledge, the study presented here is the first to evaluate this drug combination in patients with vertigo due to acute vestibular disorders. Acute vestibular loss is usually treated with several different drugs. The ideal medication should, however, suppress the sensation of vertigo, help restore normal balance, and prevent vomiting, and should not impede the normal process of recovery from the vestibular lesion.[5] The present study assessed the efficacy and tolerability of the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg in comparison with the respective monotherapies cinnarizine 20 mg and dimenhydrinate 40 mg in the treatment of vertigo due to acute unilateral vestibular loss.

PATIENTS AND METHODS

Study Population

Adult inpatients at the ENT Clinic at the University of Rostock who had vertigo due to acute unilateral vestibular failure or unilateral vestibular neuropathy were eligible to participate in the study. The diagnoses were confirmed by examination of gaze-evoked, positional, and caloric nystagmus (monitoring of side differences by means of photoelectronystagmography [PENG] and electronystagmography [ENG]). Exclusion criteria were in accordance with the fixed combination's contraindications and included convulsive seizures, suspected compressive intracranial processes, angle-closure glaucoma, prostate adenoma, Parkinson's disease, asthma, gastrointestinal ulcer, acute intoxication, severe renal insufficiency, epilepsy, and alcohol abuse. Women who were pregnant, lactating, or not practicing contraception during the study period were also excluded. Use of antivertiginous drugs other than the study medication was not permitted during the study.

Protocol

This randomized, double-blind, reference-controlled, single-center, parallel-group Phase III clinical study was conducted at the ENT Clinic, University of Rostock, Germany. It was performed in accordance with the principles of Good Clinical Practice and the recommendations of the Declaration of Helsinki (1989 revision). The study was approved by the appropriate local ethics committee. All patients were informed about the study in detail (orally and in writing) and gave their written informed consent before enrollment. Patients were randomized to 4 weeks of treatment (1 tablet 3 times daily) with the fixed combination of 20 mg cinnarizine and 40 mg dimenhydrinate, cinnarizine 20 mg per tablet, or dimenhydrinate 40 mg per tablet. All patients also received a 15% mannitol infusion as standard therapy during the first 6 days (**Figure 1**). The patients stayed in the hospital during the first week of the study period and were subsequently dismissed to continue their respective drug therapies at home. Patients underwent an entry examination (before the start of treatment), an intermediate examination (after 7 ± 2 days), and a final examination (after 28 ± 2 days). At each visit, vertigo symptoms, vegetative symptoms concomitant to vertigo, and other symptoms concomitant to vertigo were recorded.

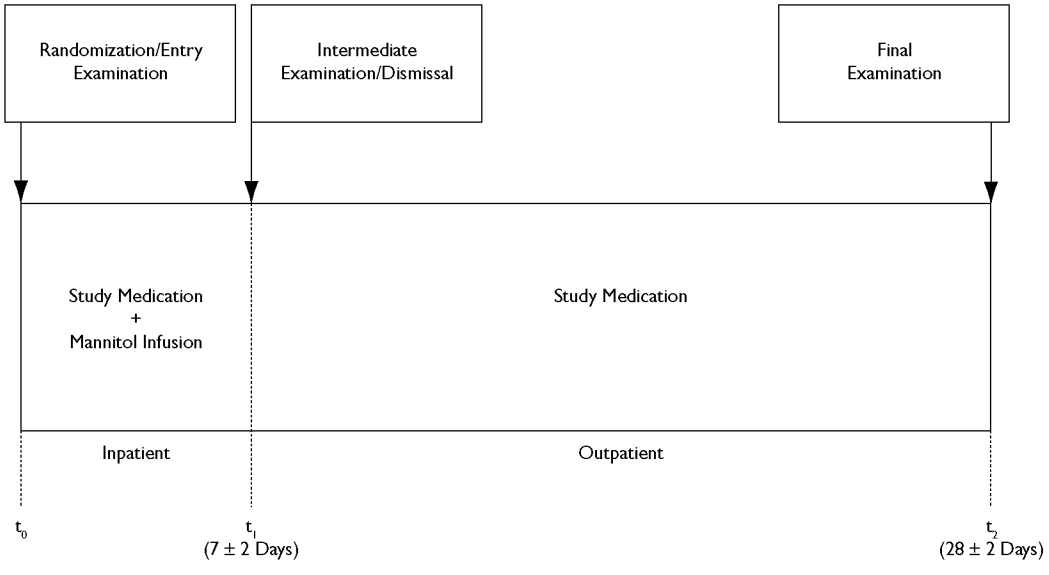

Figure 1. Schematic representation of the investigational plan. Study medication: fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg per tablet (1 tablet 3 times daily); or cinnarizine, 20 mg per tablet (1 tablet 3 times daily); or dimenhydrinate, 40 mg per tablet (1 tablet 3 times daily).

Vestibulo-ocular tests (nystagmus tests) and vestibulospinal tests (Romberg's test) were performed at each visit. Hearing was tested using pure tone audiometry at the entry and final examinations. Global efficacy and tolerability were judged by both the investigator and patient after 4 weeks of treatment. Adverse events were recorded at the intermediate and final examinations, based on direct questioning or medical findings. Furthermore, the patients were advised to contact the investigator if adverse events occurred during the course of the study. Compliance with treatment was assessed by counting the tablets returned by the patients at the end of the treatment period. During hospitalization, medication intake was controlled by the nursing staff (mouth check). Study medication was manufactured by Hennig Arzneimittel (Floersheim am Main, Germany) according to Good Manufacturing Practice. Test medication and reference medication were indistinguishable with respect to appearance, taste, weight, shape, and packaging.

Evaluation of Efficacy

Primary Efficacy Criterion

The primary criterion of efficacy was the relief of vertigo symptoms and vertigo intensity following trigger factors (ie, movements leading to vertigo symptoms) after 1 week of treatment. The patients evaluated the intensity of their vertigo symptoms using a verbal rating scale (VRS) in which 0 = no symptom, 1 = mild, 2 = moderate, and 3 = severe. Symptoms assessed at each patient visit included unsteadiness (dystasia and walking unsureness), staggering, rotary sensation, tendency to fall, lift sensation, and swaying, as well as the intensity of vertigo following 6 specific trigger factors—change of position, bowing, getting up, walking, head movements, and eye movements. A mean vertigo score, S_M, was calculated from the VRS-based quantified intensities of the aforementioned vertigo symptoms plus the quantified intensities of the vertigo following the 6 trigger factors; thus, S_M represents a parameter for the global evaluation of vertigo severity. The reduction in S_M after 1 week of treatment was the primary study outcome measure.

Secondary Efficacy Criteria

Secondary criteria of efficacy included the relief of vertigo symptoms and vertigo intensity following trigger factors after 4 weeks of treatment; relief of vegetative and other symptoms concomitant to vertigo; vestibulospinal, vestibulo-ocular, and audiometric assessments; and global efficacy.

Vegetative and Other Symptoms Concomitant to Vertigo

Vegetative symptoms concomitant to vertigo (ie, nausea, vomiting, sweating, tachycardia, and headache) were recorded by the patients. Based on the value of each of these symptoms, a mean vegetative score (V_M) was established and was analyzed the same way as S_M. In addition, other symptoms concomitant to vertigo (ie, pressure sensation in the ear, tinnitus, impaired hearing, impaired vision, ocular symptoms, and bulbar symptoms) were reported.

Vestibulospinal Tests

Vestibulospinal movement patterns of patients while performing Romberg's (standing) test were recorded using computer-aided posturography. Body sway was evaluated by means of the displacements of the gravity center as reflected by the posturography sway areas on the x and y axes. Evaluation of Romberg's test was based on the Romberg Index, which represents the ratio of the measured areas of total sway with eyes open and with eyes closed.

Vestibulo-ocular Tests

Gaze-evoked and positional nystagmus were analyzed using Frenzel's glasses. Occurrence of gaze-evoked nystagmus was examined at the main glance directions, followed by assessment of positional nystagmus by monitoring nystagmus reactions at the dorsal position with head to the right, head to the left, and sitting up.

The caloric nystagmus test was performed to determine the side of the vestibular lesion and to identify disorders of the labyrinth and the vestibular nerve. Caloric testing was done by irrigation of either ear with cool (30°C) and warm (44°C) water (100 mL for 30 seconds). Using PENG and ENG, nystagmus slow-phase velocity (SPV) as well as frequency (beats per 30 seconds) were determined during the middle 30-second period at maximum reaction. To determine the presence of a unilateral weakness, the response strength from each side was compared using Jongkees's formula.

Global Efficacy

At the end of the final visit, patients and the investigator were asked to evaluate the global efficacy of the treatment based on a VRS in which 1 = very much improved, 2 = much improved, 3 = slightly improved, and 4 = not improved.

Tolerability

The tolerability assessment was based on reports of adverse events occurring after drug intake. The events were either 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 recorded in detail at each follow-up visit and classified according to the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) body system. At the end of the final visit, patients and the investigator rated the global tolerability of the drugs based on a verbal rating scale, where 1 = very good, 2 = good, 3 = moderate, and 4 = poor.

Statistical Analysis

The statistical analysis was performed on the per-protocol population. All enrolled patients completed the study according to protocol. The primary efficacy variable was the change in S_M from baseline. The confirmatory analysis was performed in the hierarchical order (first) 1 week and (second) 4 weeks after the start of treatment. The primary efficacy variable showed a low approximation to normal distribution. Therefore, treatment groups were compared nonparametrically (Kruskal-Wallis test) at a global significance level of 0.05. In accordance with the Bonferroni correction, simultaneous comparisons between the treatment groups were performed at a significance level of $\alpha = 0.025$. Due to nonhomogeneous initial distributions, the variable S_M was subjected to analysis of covariance (ANCOVA) with adjustment of means at the end of the study using the initial values as covariates. In addition, 2-sided 95% CIs for changes from baseline between the treatment groups were determined. The changes in single vertigo symptoms were analyzed by means of exact contingency table tests. Similarly, an exploratory analysis was performed on additional secondary variables to compare changes between treatment groups during the course of the study.

RESULTS

Demographic Characteristics of Study Population

A total of 50 patients were randomized into 3 treatment groups (fixed combination, 15 patients; cinnarizine 20 mg, 17 patients; and dimenhydrinate 40 mg, 18 patients). All patients completed the study according to protocol. Treatment groups were comparable with respect to demographic characteristics, except for weight; there was a slight imbalance at the 20% significance level due to a lower minimum weight in the dimenhydrinate group ($P < 0.2$) (**Table I**). The

Table I. Demographic and clinical characteristics of the study population (N = 50).

	Fixed Combination (n = 15)	Cinnarizine (n = 17)	Dimenhydrinate (n = 18)
Sex, no. (%)			
Male	6 (40)	10 (59)	7 (39)
Female	9 (60)	7 (41)	11 (61)
Age, mean ± SD (range), y	51.47 ± 9.79 (37–66)	51.35 ± 10.76 (33–68)	53.83 ± 14.32 (31–77)
Body weight, mean ± SD (range), kg	79.20 ± 15.16 (60–117)	77.41 ± 10.20 (63–91)	72.83 ± 16.19† (52–118)
Height, mean ± SD (range), cm	168.40 ± 8.81 (155–186)	169.35 ± 7.70 (154–183)	166.94 ± 8.07 (152–185)
Body mass index,* mean ± SD (range), kg/m^2	27.73 ± 3.17 (22.31–33.82)	27.00 ± 3.18 (20.31–32.66)	25.96 ± 4.23† (19.10–34.48)

*Body mass index = body weight /(height in m)^2.
†Inhomogeneous at the 20% level with respect to the fixed combination.

study population included 27 women and 23 men. The mean age was 52.3 years and the mean body mass index was 26.9 kg/m^2. All patients had a confirmed diagnosis of acute vestibular neuropathy. A total of 28 patients reported concomitant diseases, with cardiovascular disease being the most frequently reported (~40%). Compliance was nearly 100%, and no differences between the treatment groups with respect to compliance were observed.

Clinical Efficacy

Relief of Vertigo Symptoms and Vertigo Following Trigger Factors

The fixed combination was significantly more effective than both cinnarizine 20 mg alone ($P < 0.01$) and dimenhydrinate 40 mg alone ($P < 0.01$) in reducing S_M after 1 week (**Table II**). The baseline S_M values of the fixed combination group were homogeneous with respect to the baseline scores of the reference medication cinnarizine (Kruskal-Wallis test, $P = 0.272$), but showed a slight imbalance at the 20% significance level with respect to dimenhydrinate (Kruskal-Wallis test, $P = 0.157$). Correction for initial nonhomogeneity by ANCOVA resulted in an even more pronounced difference in efficacy of the fixed combination compared with cinnarizine after 1 week of treatment ($P < 0.001$). All 3 treatments led to a strong improvement in S_M throughout the 4-week treatment period compared with the respective baseline values. However, after 4 weeks of treatment, the fixed combination resulted in significantly greater relief of vertigo symptoms than the comparator cinnarizine 20 mg without ($P < 0.05$) or with adjustment by ANCOVA ($P < 0.01$). Changes in S_M (before and after adjustment by ANCOVA) with the respective 95% CIs are shown in Table II, and 95% CIs for differences between treatment groups are presented in **Table III**.

Vestibulospinal Tests

At the entry examination, 27 of the 50 patients, equally distributed among all treatment groups, were unable to perform Romberg's test because of severe vertigo symptoms. Thus, no initial values were available for these patients. For the remaining 23 patients, the Romberg Index had homogeneous mean values between 1.00 and 1.12 in all treatment groups. Within the first week of treatment, the Romberg Index decreased markedly followed by a further, less pronounced decline during the subsequent 3 weeks in all treatment groups. The fixed combination group showed the largest reductions both after 1 and 4 weeks of treatment; however, the differences were statistically significant only compared with the dimenhydrinate group after 4 weeks ($P < 0.05$, **Table IV**). One week after the onset of treatment, the 27 patients who initially had been incapable of performing Romberg's test were able to do so. For the evaluation of Romberg Index changes for all patients during the course of the study, a hypothetical maximum index of 2.0 was set as the initial value for these 27 patients, taking into account the severity of the disease in these patients and the index values observed in the first examination

Table II. Changes in the mean vertigo score (S_M) during the course of the study.

	After 1 Week			After 4 Weeks		
	Mean Reduction	95% CI	P^*	Mean Reduction	95% CI	P^*
Fixed combination (n = 15)						
Mean change ± SD	2.09 ± 0.41	1.87–2.32		2.39 ± 0.33	2.21–2.58	
Adjusted mean†	2.12			2.41		
Cinnarizine (n = 17)						
Mean change ± SD	1.57 ± 0.46	1.33–1.80	0.003	2.11 ± 0.36	1.92–2.29	0.037
Adjusted mean†	1.56		<0.001	2.10		0.005
Dimenhydrinate (n = 18)						
Mean change ± SD	1.65 ± 0.33	1.49–1.82	0.002	2.15 ± 0.33	1.98–2.31	0.035
Adjusted mean†	1.64		0.003	2.14		0.060

*Versus fixed combination, Kruskal-Wallis test.
†Calculated after adjustment for nonhomogeneous initial distribution by analysis of covariance.

Table III. Least-squares means and 95% CIs for differences in mean vertigo score (S_M) between the fixed combination and comparative study drugs.

	Least-squares Mean*	95% CI
Fixed combination vs cinnarizine	0.36	0.16–0.56
Fixed combination vs dimenhydrinate	0.29	0.12–0.47

*Mean difference adjusted for baseline values (analysis of covariance) of baseline minus 1 week.

in the remaining study population (maximum = 1.91). The resulting initial values in the complete patient population (n = 50) showed a homogeneous distribution among the treatment groups with mean values between 1.49 and 1.61. Analyses that included the 27 patients who had not performed the initial Romberg test revealed the same results as analyses with patients tested at all 3 visits (n = 50).

Vegetative Symptoms Concomitant to Vertigo

The baseline V_M of the fixed combination group was homogeneous compared with the V_M baseline values of the reference medications cinnarizine and dimenhydrinate. After 1 week of treatment, the V_M of all 3 groups decreased to ~10% of the initial value, reflecting a marked relief of the patients' vegetative symptoms. During the next 3 weeks, vegetative symptoms subsided almost completely (**Table V**). No significant differences between the effects of the 3 medications were observed.

Other Symptoms Concomitant to Vertigo

The complaints of tinnitus, impaired hearing, and pressure sensation in the ear were homogeneously distributed among treatment groups at baseline. These symptoms were reported by 1 to 3 patients per treatment group except for tinnitus in the cinnarizine group, which was reported by 6 patients at the entry examination. Due to the low frequency of occurrence, an analysis of changes with treatment was not appropriate.

Vestibulo-ocular Tests

Initially, the entire patient population presented with a pronounced spontaneous nystagmus (not shown). Similar to the mean vertigo score S_M, spontaneous nystagmus was markedly reduced from 100% to 80% after 1 week and to 28% at the end of 4 weeks' treatment. No significant differences were observed between treatment groups. Positional nystagmus could not be assessed at the first and intermediate examinations in 100% and 72% of the patients, respectively, due to superimposition by spontaneous nystagmus. Analysis of the available data showed no statistically significant differences between treatment groups (not shown). Evaluation of caloric nystagmus was based on SPV measured by means of PENG and ENG. According to the characteristics of the underlying disease, the patients initially presented with hyporeflexia or areflexia on the affected side. The corresponding SPV values ranged from 0 to 11.4 deg/s. The treatment groups were homogeneous with respect to the initial distribution of mean SPV values at either the affected or unaffected side. As shown in **Figure 2**, caloric nystagmus at the affected side markedly improved with treatment. The initial, very low SPV increased during treatment, resulting in means of 5.98 ± 4.13 deg/s after 1 week and 9.28 ± 6.33 deg/s after 4 weeks of treatment, with no statistically significant differences between the treatment

Table IV. Changes in Romberg Index* during the course of the study.

	After 1 Week		After 4 Weeks	
	Mean Reduction ± SD	P†	Mean Reduction ± SD	P†
Fixed combination (n = 15)	0.90 ± 0.52		1.25 ± 0.59	
Cinnarizine (n = 17)	0.71 ± 0.43	0.406	0.96 ± 0.56	0.059
Dimenhydrinate (n = 18)	0.72 ± 0.54	0.347	1.01 ± 0.59	0.043

*With estimated maximal Romberg Index of 2 for missing values at baseline.
†Versus fixed combination, Kruskal-Wallis test.

Table V. Changes in mean vegetative score (V_M) during the course of the study.

	After 1 Week		After 4 Weeks	
	Mean Reduction ± SD	P^*	Mean Reduction ± SD	P^*
Fixed combination (n = 15)	1.68 ± 0.41		1.77 ± 0.45	
Cinnarizine (n = 17)	1.53 ± 0.51	0.447	1.71 ± 0.58	0.747
Dimenhydrinate (n = 18)	1.60 ± 0.41	0.585	1.78 ± 0.49	0.870

*Versus fixed combination, Kruskal-Wallis test.

groups. The increase in mean SPV, indicating the recovery of the nystagmus reaction, was significant both after 1 and 4 weeks ($P < 0.001$ in all groups). On the other hand, SPV values at the contralateral side remained unaffected during the course of treatment.

Global Efficacy

The global efficacy judgments by the investigator and the patients were very similar, and corresponded with the marked improvements in vertigo symptoms during the course of therapy. In both cases, the statistical analysis confirmed the significantly greater efficacy of the fixed combination with respect to cinnarizine and the absence of a significant difference in efficacy compared with dimenhydrinate (**Table VI**).

Tolerability

All 3 treatments proved to be well tolerated. No serious adverse events (AEs) were reported during the study. The rate of nonserious AEs was consistent across treatment groups; all AEs were of mild to moderate intensity and had subsided by the end of treatment. None of the patients withdrew due to AEs, and all patients completed the study according to protocol within 28 ± 2 days. Overall, 14 of 50 patients (28.0%) reported AEs. The rate of AEs was 26.7% in

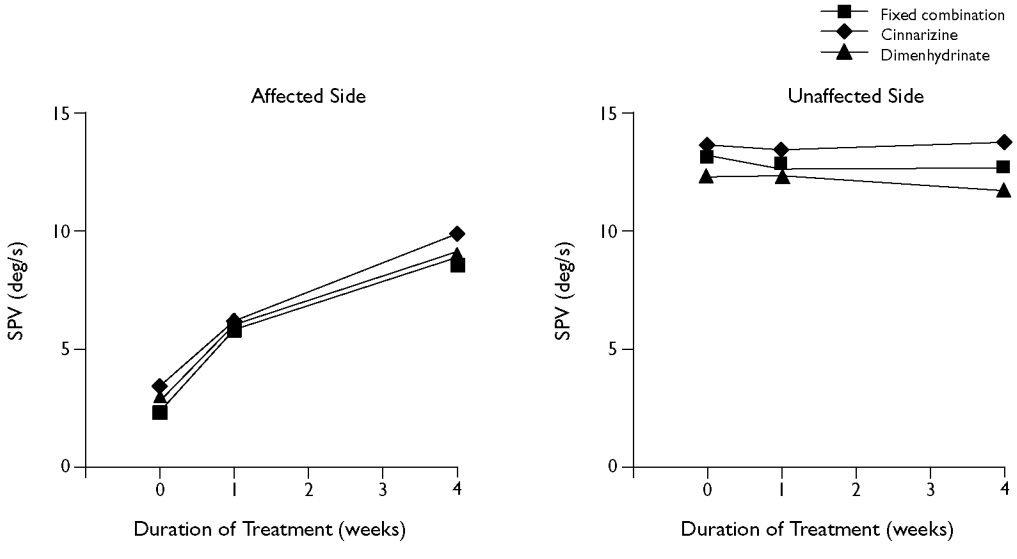

Figure 2. Caloric nystagmus on the affected and unaffected sides of vestibular loss. Evaluation was based on the velocity of the slow phase of nystagmus (slow-phase velocity [SPV] in degrees per second), which was determined automatically by a calculation program that received the data from the recording apparatus.

Table VI. Global efficacy as judged by the investigator and patients after 4 weeks of therapy.

	No. (%) of Patients			
	Very Much Improved	Much Improved	Slightly Improved	*P*
Investigator's judgment				
Fixed combination	6/15 (40.0)	7/15 (46.7)	2/15 (13.3)	
Cinnarizine	–	14/17 (82.4)	3/17 (17.6)	0.010
Dimenhydrinate	7/18 (38.9)	9/18 (50.0)	2/18 (11.1)	1.000
Patients' judgment				
Fixed combination	9/15 (60.0)	5/15 (33.3)	1/15 (6.7)	
Cinnarizine	1/17 (5.9)	11/17 (64.7)	5/17 (29.4)	0.001
Dimenhydrinate	8/18 (44.4)	8/18 (44.4)	2/18 (11.1)	0.686

the fixed combination group (4/15 patients, 5 AEs), 23.5% in the cinnarizine group (4/17 patients, 6 AEs), and 33.3% in the dimenhydrinate group (6/18 patients, 8 AEs), with no significant differences between groups (**Table VII**). The most frequent AE across the study population was fatigue, followed by headache. Since these symptoms are frequently caused by the underlying disease, it remains unclear whether they represented adverse drug reactions or symptoms of acute vestibular loss. The tolerability of the treatments is underscored by the patients' judgments of treatment tolerability at the end of the study. In the fixed combination group, 100% of patients rated the tolerability of treatment as very good or good; the corresponding rates in the cinnarizine and dimenhydrinate groups were 82.4% and 94.4%, respectively (**Table VIII**).

DISCUSSION

Patients with acute vestibular loss are incapable of maintaining their balance and experience intense vertigo and strong vegetative symptoms, including nausea and vomiting. Due to the severity of symptoms, patients are generally confined to bed rest for diagnosis and treatment. The standard therapy consists primarily of bed rest and infusion with drugs such as

Table VII. Adverse events in the randomized population (N = 50).

Adverse Event (COSTART Code)	Body System (COSTART)	Fixed Combination (n = 15)	Cinnarizine (*P* vs fixed combination) (n = 17)	Dimenhydrinate (*P* vs fixed combination) (n = 18)	Total (%)
Tiredness*	Nervous system	3	1 (0.32)	4 (1.0)	8 (16.0)
Dryness of mouth	Digestive system	–	1 (1.0)	1 (1.0)	2 (4.0)
Abdominal pressure sensation	Digestive system	–	–	1 (1.0)	1 (2.0)
Headache	Body	2	3 (1.0)	2 (1.0)	7 (14.0)
Tachycardia	Cardiovascular system	–	1 (1.0)	–	1 (2.0)
Total		5	6	8	19
No. (%) of patients reporting adverse event		4/15 (26.7)	4/17 (23.5)	6/18 (33.3)	14/50 (28.0)

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.
*Tiredness has to be coded as "somnolence" according to the COSTART code.

Table VIII. Judgment of tolerability by investigator and patients after 4 weeks of treatment.

	No. (%) of Patients			
	Very Good	Good	Moderate	*P*
Investigator's judgment				
Fixed combination	12/15 (80.0)	3/15 (20.0)	–	
Cinnarizine	9/17 (52.9)	7/17 (41.2)	1/17 (5.9)	0.191
Dimenhydrinate	11/18 (61.1)	6/18 (33.3)	1/18 (5.6)	0.558
Patient's judgment				
Fixed combination	11/15 (73.3)	4/15 (26.7)	–	
Cinnarizine	7/17 (41.2)	7/17 (41.2)	3/17 (17.6)	0.120
Dimenhydrinate	11/18 (61.1)	6/18 (33.3)	1/18 (5.6)	0.843

pentoxyphylline, cortisone, or mannitol. However, patients often continue to experience strong vertigo symptoms during compensation and need additional symptomatic relief, especially within the first week after vestibular failure. Therefore, the simultaneous administration of antivertiginous medication is often useful. In the present study, the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg provided this additional benefit for patients with acute vestibular loss. The combination was significantly more effective than the monotherapy components in reducing vertigo symptoms within the first week of treatment ($P < 0.01$). Although the major benefit of this combination therapy is the rapid (within the first week) improvement of vertigo, long-term therapeutic effects are also evident. After 4 weeks of treatment, vertigo symptoms as well as vegetative symptoms concomitant to vertigo resolved almost completely across the entire study population, with no major differences between the treatment groups. However, the fixed combination was still significantly more effective than cinnarizine in reducing vertigo symptoms ($P < 0.01$). In addition, Romberg's test confirmed the therapeutic advantage of the fixed combination compared to the reference therapies after 4 weeks, demonstrating a statistically significant difference compared with dimenhydrinate ($P < 0.05$). The greater efficacy of the fixed combination compared with its single active components might be explained pharmacologically by the dual mechanism of action of the combination. Cinnarizine, a calcium-channel blocker,[20] improves cochlear circulation and decreases labyrinth excitability at peripheral vestibular sites.[11–14] Dimenhydrinate is a centrally acting H_1 antihistamine. The combination, therefore, provides antivertiginous activity at both peripheral and central sites, resulting in a synergistic effect. The effects of the fixed combination and the single-agent components were accompanied by the effects of the standard infusion therapy—reconstitutive processes and central compensation. The partial recovery of the caloric nystagmus at the affected side as well as the gradual decrease in spontaneous nystagmus (both showing no significant differences between treatment groups) may be explained by regenerative processes. Additional studies that include a placebo control are required to determine the contributions of the fixed combination or its components to these processes. With respect to compensation, 2 recent studies demonstrated that the combination product only marginally affects vigilance, suggesting that central compensation processes are not suppressed.[21,22] The rate of AEs in the fixed combination group was similar to those found in the reference groups, and all patients rated the tolerability of the fixed combination as good or very good. Thus, the combination of cinnarizine 20 mg and dimenhydrinate 40 mg has the favorable tolerability of the low-dose single agents, but has greater clinical efficacy. Since no placebo group was included in this study, it remains unclear whether the reported AEs were drug-specific. Nevertheless, the benefit/risk ratio of the fixed combination exceeded that of both reference medications. The results in patients with acute vestibular vertigo are consistent with those from previous studies, which demonstrated the antivertiginous efficacy and good tolerability of the fixed combi-

nation in the treatment of patients with chronified vertigo of peripheral vestibular, central vestibular, or combined peripheral/central vestibular origin, as well as Ménière's disease.[17–19,23] The knowledge gained from these investigations, together with the results presented herein, underscore the therapeutic advantage of the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg in the treatment of acute or chronified vertigo due to vestibular failure.

CONCLUSIONS

In this study, the fixed combination of cinnarizine 20 mg and dimenhydrinate 40 mg proved to be significantly more effective than the respective monotherapies in reducing vertigo due to acute vestibular loss within the first week of treatment while supporting compensation processes. Hence, this fixed combination represents not only a well-established treatment for chronic vestibular vertigo, but also an effective treatment option for acute vestibular vertigo.

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