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Fixed Combination of Cinnarizine and Dimenhydrinate Versus Betahistine Dimesylate in the Treatment of Ménière's Disease: A Randomized, Double-Blind, Parallel Group Clinical Study

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Abstract: In a randomized, double-blind clinical study, we evaluated the efficacy and tolerability of the fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg (Arlevert [ARL]) in comparison to betahistine dimesylate (12 mg) in 82 patients suffering from Ménière's disease for at least 3 months and showing the characteristic triad of symptoms (paroxysmal vertigo attacks, cochlear hearing loss, and tinnitus). The treatment (one tablet three times daily) extended to 12 weeks, with control visits at 1, 3, 6, and 12 weeks after drug intake. The study demonstrated for both the fixed-combination ARL and for betahistine a highly efficient reduction of vertigo symptoms in the course of the 12 weeks of treatment; however, no statistically significant difference between the two treatment groups could be established. Similar results were found for tinnitus (approximately 60% reduction) and for the associated vegetative symptoms (almost complete disappearance). Vestibulospinal reactions, recorded by means of craniocorpography, also improved distinctly, with a statistically significant superiority of ARL versus betahistine ($p < .042$) for the parameter of lateral sway (Unterberger's test). The caloric tests (electronystagmography) showed only minor changes for both treatment groups in the course of the study. A statistically significant improvement of hearing function of the affected ear ($p = .042$) was found for the combination preparation after 12 weeks of treatment. The tolerability was judged by the vast majority of patients (97.5%) in both groups to be very good. Only one patient (betahistine group) reported a nonserious adverse event, and two betahistine patients did not complete the study. In conclusion, the combination preparation proved to be a highly efficient and safe treatment option for Ménière's disease and may be used both in the management of acute episodes and in long-term treatment. Efficacy and safety were found to be similar to the widely used standard therapy with betahistine.

Key Words: betahistine; cinnarizine and dimenhydrinate; Ménière's disease; vertigo

Ménière's disease, described for the first time in 1861 by Prosper Ménière, is characterized by a triad of symptoms in a characteristic, classic pattern of episodic vertigo, tinnitus, and fluctuating sensory hearing loss [1–3]. Frequently associated symptoms are aural fullness and vegetative symptoms, such as nausea and vomiting. The causal association of the disease with endolymphatic hydrops is widely accepted [4]. The complete clinical picture usually develops only after several years, which makes it more difficult to establish the diagnosis in earlier stages. The diagnosis is based mainly on anamnestic data typical for Ménière's disease.

Vertigo is believed to be the most distressing symptom for affected patients. Frequency and severity of the

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vertigo attacks usually increase as the disease progresses. The vertigo attacks (predominantly rotational vertigo) occur suddenly without warning—albeit in a majority these are preceded by an "aura," as in epilepsy, with aural fullness, tinnitus, and nausea for 10–30 minutes—and last for several minutes to hours; they recur after days, weeks, or months, followed by episodes with weak or no symptoms (remission).

Surgical treatment of Ménière's disease is indicated only in severe cases and after attempts of conservative therapy have failed. Medical treatment is composed of a great variety of agents, including vasodilators and vestibular suppressants [5,6]. The histamine derivative betahistine shows a controlling effect on the capillary blood flow of the labyrinthine vascular system [7] and, at doses of 24–48 mg/day, is widely considered as first choice for prophylactic treatment of Ménière's disease [6,8]. Conversely, vestibular suppressants, such as dimenhydrinate, have proven to be very effective in the management of acute Ménière's attacks owing to their antivertiginous, antiemetic, and sedative properties [5,6,9].

The antivertiginous drug Arlevert (ARL), a fixed combination of the calcium antagonist cinnarizine (20 mg per tablet) and the antihistamine dimenhydrinate (40 mg per tablet), has been successfully used for a long time in the treatment of vertigo of various origins and has been tried and tested in numerous randomized, double-blind clinical trials [6,10,11]. The combination preparation is highly effective in both central and peripheral vestibular disorders owing to its dual mechanism of action. A synergistic effect of cinnarizine and dimenhydrinate has been proposed [12].

Cinnarizine primarily leads to a cerebral and cochlear increase of perfusion [13,14] and acts as a vestibular sedative through inhibition of the calcium influx into the vestibular sensory cells [15]. Dimenhydrinate acts as an antihistamine with anticholinergic properties and exhibits anivertiginous and antiemetic effects. Owing to these pharmacological properties of the components, the fixed combination is expected to show a favorable effect in the treatment of Ménière's disease: cinnarizine, with a prophylactic effect by means of improvement of inner ear circulation, and dimenhydrinate, intended to alleviate acute vertigo attacks through its antivertiginous, antiemetic, and sedative effects.

In our study, the efficacy and safety of the fixed combination of cinnarizine and dimenhydrinate was investigated in patients suffering from Ménière's disease. Betahistine was chosen as the reference drug, as it is a generally accepted standard treatment, especially in the prophylactic treatment of Ménière's disease.

PATIENTS AND METHODS

Patient Population

The patient population consisted of 82 male and female white outpatients (age >30 years) suffering from Ménière's disease for at least 3 months. Included were only patients showing the complete triad of symptoms (i.e., paroxysmal attacks of vertigo, cochlear hearing loss, and tinnitus) and having experienced a minimum of three vertigo attacks occurring during the 3 months prior to enrollment, one of which had to be either moderate or severe (on a 3-point scale, including gradations of mild, moderate, and severe). Exclusion criteria were convulsive seizures, suspicion of compressive intracranial processes, narrow-angle glaucoma, prostate adenoma with residual urine, Parkinson's disease, asthma, gastrointestinal ulcer, acute poisoning, severe renal insufficiency, epilepsy, and alcohol abuse. Further exclusion criteria included suspected acoustic neurinoma, apparent infection of the inner ear, caloric inexcitability (areflexia), vertigo due to unsolved organic primary disease, previous surgical treatment for Ménière's disease, and benign paroxysmal positional vertigo. Pregnant women and nursing mothers and women of child-bearing potential who were not taking adequate contraceptive measures were not allowed to participate in the study. Concomitant medications, such as aminoglycoside antibiotics, monoamine oxidase inhibitors, tricyclic antidepressants, parasympatholytics, glucocorticoids, and heparin were not permitted.

Patients taking benzodiazepines, acetylsalicylic acid, or piracetam were eligible for enrollment. Antivertiginous and or cerebrovascularly active drugs had to be discontinued prior to the start of treatment (1-week washout phase). In cases of flunarizine, the washout phase was extended to 3 months.

Study Design

The study was carried out according to a randomized, double-blind, reference-controlled design with two parallel groups. It was conducted in accordance with the Declaration of Helsinki and the guidelines for good clinical practice. The study documents were reviewed and approved by an independent ethics committee and by competent health authorities. All patients provided written informed consent prior to enrollment in the study.

The 82 patients were randomly assigned to receive either the fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg (i.e., ARL) or the reference medication, betahistine dimesylate, 12 mg three times daily for 12 weeks. The two agents were made to appear identical, to facilitate double-blind randomization. For

randomization, a computer-generated block sequence was used, which ensured equal distribution of the patients into the two treatment groups. The entry examination took place on day 1 (before drug intake), followed by three intermediate examinations after 1, 3, and 6 weeks and a final examination after 12 weeks. On the occasion of all visits, vertigo anamnesis tests (including concomitant symptoms), vestibulospinal tests (Unterberger's and Romberg's tests) registered by craniocorpography (CCG), registration of spontaneous positional nystagmus (Frenzel's glasses), and pure-tone audiometry were carried out. In addition, that caloric nystagmus test (electronystagmography [ENG]) was performed at day 1 and after 3 and 12 weeks of treatment. Both patients and investigator gave a global judgment of the efficacy and tolerability of the study medication after 1, 3, 6, and 12 weeks of treatment. Compliance was controlled on the basis of the number of tablets returned by the patients at the end of treatment.

Primary Efficacy Criterion

The patients were asked to judge the intensity of vertigo and concomitant symptoms on a visual analog scale with possible ratings between 0 (no symptom) and 4 (very strong symptom). From the ratings for six vertigo symptoms (dystasia and walking unsteadiness, staggering, rotary sensation, tendency to fall, lift sensation, and blackout) and six vertigo trigger factors (change of position, bowing, getting up, driving by car or train, head movements, and eye movements), a mean vertigo score (S_M) was calculated, with theoretical values between 0 (no symptom at all) and 4 (all 12 symptoms present with maximum intensity). The change of S_M in the course of the 12 weeks of treatment was used as the primary efficacy criterion.

Secondary Efficacy Criteria

Concomitant symptoms of vertigo (assessed by visual analog scale), vestibulospinal tests (assessed by CCG), ENG tests, and audiometry and a global judgment by both patient and investigator were used as secondary criteria of efficacy. Concomitant vegetative symptoms (nausea, vomiting, sweating, and tachycardia) and further symptoms related to the disease (tinnitus, impaired hearing, aural fullness, headache, and impaired vision) were registered.

Vestibulospinal (Unterberger's and Romberg's) tests were registered by CCG [16, 17], as previously described [10,18]. The following parameters were determined: Unterberger's test—linear displacement, lateral sway, angular deviation, body spin; Romberg's test—anteroposterior and lateral sway. Spontaneous and positional nystagmus were assessed by means of Frenzel's glasses. The caloric test with ENG registration was performed according to standard procedures (irrigation of 20 ml water at 30° and 44°C for 30 seconds) [18]. Nystagmus frequency—which served for calculation of caloric weakness and directional preponderance, according to Jongkees [19]—as well as amplitude and culmination area were determined. Standard pure-tone threshold audiometry was performed at frequencies of 250, 500, 1,000, and 2,000 Hz.

Global judgment of efficacy by investigator and patient was performed by means of a 5-point rating scale with possible ratings of "very much improved," "much improved," "slightly improved," "not improved," and "deteriorated." The same rating scale applied to the parameter of "impairment of fitness for work."

Evaluation of Tolerability

The safety of the study medications was assessed by registration of adverse events on the occasion of each follow-up visit; in addition, systolic and diastolic blood pressure was measured at each visit. Adverse events were classified according to World Health Organization Adverse Reaction Terminology by using the "system organ class" and the "preferred term."

Furthermore, investigator and patient judged the general tolerability of the treatment on the occasion of each follow-up visit using a 4-point rating scale with possible ratings of "very good," "good," "moderate," and "poor."

Statistical Analysis

Statistical analysis was performed on the basis of the per-protocol population, including all patients who completed the study without any protocol deviation (n = 80). The intent-to-treat analysis included data of only 1 additional patient (n = 81) and is therefore not considered further.

Comparability of demographic and anamnestic variables between treatment groups before the start of treatment was assessed at the 20% significance level using the Wilcoxon-Mann-Whitney test (U-test) in case of quantitative data and Fisher's exact test in case of categorical data, as appropriate. Analysis of primary and secondary efficacy variables was based on changes from baseline, as evaluated at 1, 3, 6, and 12 weeks after the start of treatment, with special consideration of the S_M as a global parameter for vertigo intensity. The change of S_M in the course of the 12-week treatment phase was used as the primary criterion of efficacy.

Differences between ARL and betahistine were analyzed nonparametrically by the Wilcoxon-Mann-Whitney

test (U-test) at a significance level of $\alpha = 0.05$. Categorical (efficacy and safety) variables were descriptively compared by means of Fisher's exact test. Analysis of changes from baseline within a treatment group was done by the Wilcoxon signed rank test.

RESULTS

Disposition of Patients and Demographic Data

Eighty-two patients were randomly assigned to treatment and were valid for safety analysis. One patient of the betahistine group did not return to any subsequent control visit (owing to an adverse event) and was not valid for the intent-to-treat analysis. One other patient of the betahistine group discontinued the study after the second intermediate examination (week 3) for unknown reasons. All other patients (n = 80) completed the study with no protocol violations and were therefore valid for the per-protocol analysis.

The patients in the two treatment groups were comparable with regard to demographic characteristics (Table 1). The study population included 39 male and 43 female patients, with a mean age of approximately 50 years in both groups. The body mass index indicated a slight tendency to being overweight. On average, the enrolled patients suffered for 6–7 years (5 months–29 years) from Ménière's disease, the manifestation being approximately 65% unilateral and 35% bilateral, which is in accord with data found in the literature [20]. The vast majority of the patients (78 of 82) had been pretreated with antivertiginous drugs, some with betahistine (38 patients), cinnarizine (6 patients), and the combination preparation (4 patients). Within the 3 months prior to the start of treatment, the patients randomly assigned into the ARL group experienced, on average, seven vertigo attacks (mean duration, 4.9 hours), and those in the betahistine group experienced five attacks (mean duration, 4.5 hours; see Table 1).

Table 1. Demographic and Anamnestic Data of the Patient Population

Variable	ARL (n = 40)	Betahistine (n = 42)
Age (yr.)[a]	50.1 ± 10.2	49.5 ± 12.0
Gender (male/female)[b]	21/19	18/24
Body mass index (kg/m^2)[a]	26.2 ± 3.3	25.8 ± 3.3
Duration of disease (mo.)[a]	73.3 ± 67.4	85.3 ± 80.2
Unilateral/bilateral disease (%)	65.0/35.0	66.7/33.3
Number of attacks[a] (within 3 mo. before enrollment)	7.2 ± 6.6	5.4 ± 3.3
Medical pretreatment (% of patients)	97.5%	95.2%

ARL = Arlevert (cinnarizine-dimenhydrinate).
[a] Mean ± standard deviation.
[b] Number of patients.

The severity of the attacks was stated as mild, moderate, or severe in a ratio of approximately 1:7:6. Nearly one-third of the patients had concomitant diseases, most frequently hypertension, and antihypertensives were the most frequent concomitant medication.

Clinical Efficacy

In the course of the 12-week treatment, both drugs led to a marked reduction of S_M from initially approximately 2.4 (homogenous distribution of baseline values; $p > .2$) to 0.40 ± 0.42 and 0.31 ± 0.31 (Fig. 1) for the cinnarizine-dimenhydrinate combination and the betahistine, respectively. This represents a highly significant reduction of the S_M (primary criterion of efficacy) by more than 80% ($p < .001$, Wilcoxon signed rank test). However, no statistically significant difference could be established between the combination preparation and betahistine. Regarding the single symptoms, very similar results were found. For instance, rotational vertigo was reduced from approximately 3.2 (on a scale from 0 to 4) for either medication to 0.55 (combination) and 0.38 (betahistine), both highly significant reductions ($p < .001$) for each medication (Table 2) but without a statistically significant difference between the two medications.

Tinnitus, typically associated with Ménière's disease, showed a relatively high initial mean score of approximately 3.3 in both treatment groups (Fig. 2). Similar to the findings for vertigo, tinnitus showed highly significant improvements in the course of the therapy with both the combination and betahistine (approximately 60% reduction; $p < .001$) but, again, no signifi-

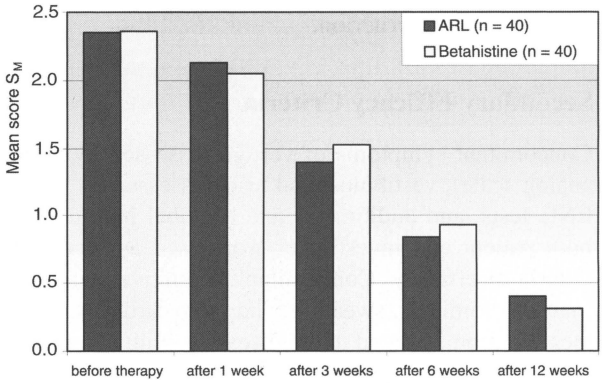

Figure 1. Vertigo symptoms (mean score [S_M]) in the course of a 12-week treatment with the fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg (ARL) or betahistine dimesylate, 12 mg, in Ménière's disease. The mean decreases in S_M in each therapy group were highly significant at all times of assessment ($p < .001$, Wilcoxon signed rank test) but with no statistically significant difference between the therapy groups ($p > .05$, Mann-Whitney U-test).

Table 2. Cardinal Symptoms of Ménière's Disease in the Per-Protocol Population

Symptom	ARL (n = 40)	Betahistine (n = 40)	*p* Value[a]
Rotary sensation			
Mean score before therapy	3.18 ± 0.55	3.15 ± 0.41	.525
Change from baseline after 12 weeks	−2.63 ± 0.93[b]	−2.78 ± 0.73[b]	.627
Tinnitus			
Mean score before therapy	3.29 ± 0.44	3.25 ± 0.48	.516
Change from baseline after 12 weeks	−1.98 ± 1.04[b]	−1.86 ± 0.76[b]	.666
Hearing loss			
Mean score before therapy	3.08 ± 0.64	3.05 ± 0.74	.918
Change from baseline after 12 weeks	−1.88 ± 1.18[b]	−1.74 ± 0.93[b]	.639
Aural fullness			
Mean score before therapy	2.93 ± 0.58	2.78 ± 0.88	.708
Change from baseline after 12 weeks	−2.21 ± 1.07[b]	−1.89 ± 1.02[b]	.098

ARL = Arlevert (cinnarizine-dimenhydrinate).
[a] Arlevert versus betahistine, Mann-Whitney U-test.
[b] Change from baseline significant at $p < .001$, Wilcoxon signed rank test.
Note: Mean score ± standard deviation before therapy and mean change (decrease) ± standard deviation after 12 weeks of therapy.

cant difference could be established between the treatments (see Table 2). Comparable results were obtained for the patients' subjective assessment of impaired hearing and aural fullness (see Table 2). Furthermore, headache was distinctly reduced in the course of the 12-week treatment, whereas none of the patients complained about impaired vision.

The score of the mean vegetative symptoms, including nausea, vomiting, sweating, and tachycardia, also markedly improved during the treatment, with statistical significance reached as early as at the end of the first week of therapy (see Fig. 1). In both groups, the vegetative symptoms had nearly completely subsided by the end of the 12-week treatment period. The statistical analysis showed highly significant changes *within* each group from the first week ($p < .001$) but no statistically significant difference *between* the two treatment groups at any time. The same holds for the single symptoms (data not shown).

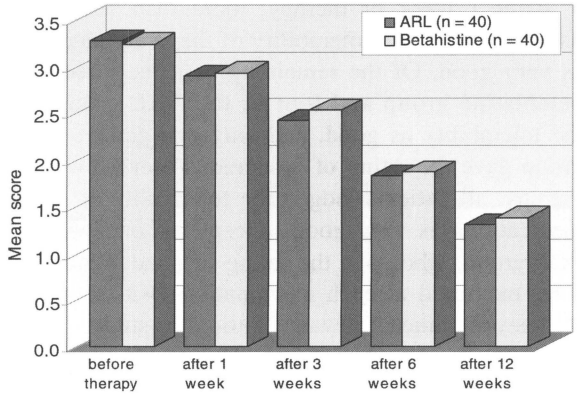

Figure 2. Tinnitus (mean score) in the course of a 12-week treatment with a fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg (ARL) or betahistine dimesylate, 12 mg, in Ménière's disease. The mean reductions in the subjective scores in each therapy group were highly significant at all times of assessment ($p < .001$, Wilcoxon signed rank test) but with no statistically significant difference between the therapy groups ($p > .05$, Mann-Whitney U-test).

The subjective judgment of vertigo symptoms by the patients was corroborated by the results of the vestibulospinal tests (i.e., Unterberger's and Romberg's tests), both registered by means of CCG. All six test parameters improved highly significantly in the course of the 12-week treatment, with mean reductions of approximately 40–60%. In particular, the parameter of lateral sway (Unterberger's test) in the ARL group decreased to a significantly greater extent during the 12-week treatment period as compared to the symptom in the betahistine group ($p = .042$). The other parameters showed no significant difference between the two treatments (Table 3).

Spontaneous nystagmus was displayed by three patients in the ARL group and two patients in the betahistine group before the start of treatment. Only one patient (in the ARL group) still presented spontaneous nystagmus after the 12-week treatment period. Positional nystagmus was initially present in 9 (of 40) patients of the ARL group (22.5%) and in 5 (of 40) patients of the betahistine group (12.5%). This number decreased to three (7.5%) and one (2.5%) after 12 weeks of therapy with ARL and betahistine, respectively. Statistical testing revealed no significant difference between the treatments.

The results obtained from the caloric nystagmus tests were inconclusive. Nystagmus frequencies and amplitudes were mostly within the normal range before, during, and after treatment. Caloric weakness and directional preponderance did not change significantly under either treat-

Table 3. Vestibulospinal Testing (Craniocorpography) Results

Variable	ARL (n = 40)	Betahistine (n = 40)	*p* Value[a]
Unterberger's test			
Lateral sway (cm)			
Before start of therapy	17.55 ± 4.33	15.69 ± 4.86	0.052
Change from baseline after 12 weeks of therapy	−6.73 ± 4.22[b]	−4.82 ± 3.63[b]	0.042
Angular deviation (degrees)			
Before start of therapy	44.98 ± 22.75	50.13 ± 26.96	0.373
Change from baseline after 12 weeks of therapy	−22.38 ± 3.14[b]	−29.82 ± 25.71[b]	0.988
Romberg's test			
Lateral sway (cm)			
Before start of therapy	8.20 ± 4.00	8.55 ± 5.85	0.594
Change from baseline after 12 weeks of therapy	−3.48 ± 3.48[b]	−3.03 ± 4.13[b]	0.283
Anteroposterior sway (cm)			
Before start of therapy	9.00 ± 4.52	8.48 ± 4.94	0.402
Change from baseline after 12 weeks of therapy	−4.38 ± 4.17[b]	−3.38 ± 3.88[b]	0.448

ARL = Arlevert (cinnarizine-dimenhydrinate).
[a] Arlevert versus betahistine, Mann-Whitney U-test.
[b] Change from baseline significant at $p < .001$, Wilcoxon signed rank test.
Note: Mean values ± standard deviation before therapy and mean change (decrease) ± standard deviation after 12 weeks of therapy.

ment. In patients with unilateral disease, the affected ear showed a lower excitability than did the nonaffected ear.

In pure-tone audiometry, patients with unilateral disease showed an initial mean hearing loss on the side of the affected ear of approximately 40 dB, which was significantly reduced in the course of the 12-week treatment in patients belonging to the ARL group ($p = .042$) but not in patients belonging to the betahistine group. Hearing loss on the nonaffected side was initially approximately 13 dB in patients in both groups and remained largely unaffected by either treatment. In patients with bilateral disease, the hearing loss was initially approximately 44 dB in either group and showed no significant changes in the course of therapy. No statistically significant difference between the two treatment groups could be observed in any case.

Finally, the global assessments of efficacy by both the investigator (data not shown) and the patients were largely in line with the distinct improvements of the S_M and associated symptoms in the course of therapy. After 1 week of treatment, more than one-half of the patients in each group stated an overall improvement in their health condition. After completion of the treatment (12 weeks), all patients, except one in the ARL group, experienced a general improvement, the distribution of the ratings "very much improved," "much improved," and "slightly improved" being 20.0, 62.5, and 15.0% in the ARL group and 32.5, 47.5, and 20.0% in the betahistine group. There was, however, no statistically significant difference between the treatment groups.

Even slightly better results were obtained for the parameter of "impairment of fitness for work." Already after 1 week, more than two-thirds of the patients stated an improvement and, after 12 weeks of treatment, 35 (of 40) patients (87.5%) in the ARL group and 36 (of 40) patients (90.0%) in the betahistine group assessed this parameter as either "much improved" or "very much improved."

Safety

Both the combination preparation and betahistine were very well tolerated. Only one patient (in the betahistine group) reported a nonserious adverse event (neurotic symptoms, judged by the investigator as not being related to the study medication), which was the reason for the retreat within the first week of the study (dropout).

After 1 week of therapy, more than 90% of the patients judged the tolerability of the study medication as very good. Of the remaining patients, three of the betahistine group and four of the ARL group rated the tolerability as good, and only one patient in each group gave the rating of moderate. After 12 weeks of therapy, all patients judged the tolerability of the two medications as very good, except for one patient in each group, who gave the rating of good. Blood pressure, measured at each examination visit, showed no changes of clinical relevance during the study.

DISCUSSION

The results of our study demonstrate a high antivertiginous efficacy and good tolerability of the fixed combination of cinnarizine and dimenhydrinate in the treatment of patients with Ménière's disease. Because severe vertigo sensations are usually the most distressing complaint of patients suffering from Ménière's disease, a

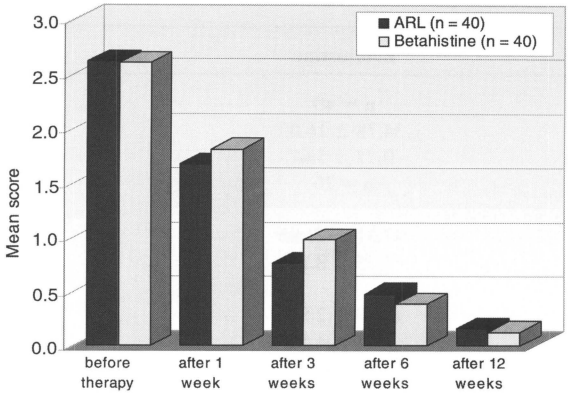

Figure 3. Vegetative symptoms (mean score [V_M]) in the course of a 12-week treatment with a fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg (ARL) or betahistine dimesylate, 12 mg, in Ménière's disease. Scores for the symptoms of nausea, vomiting, sweating, and tachycardia were averaged to a mean vegetative score per patient. The mean decreases in V_M in each therapy group were highly significant at all times of assessment ($p < .001$, Wilcoxon signed rank test) but with no statistically significant difference between the therapy groups ($p > .05$, Mann-Whitney U-test).

vertigo score, S_M (mean score of vertigo symptoms and trigger factors), was chosen as the primary efficacy variable. Both the fixed combination and betahistine led to a highly significant reduction of S_M by more than 80% in the course of the 12-week therapy (see Fig. 1). Similar results were found for the other main symptoms of tinnitus (see Fig. 2), hearing loss, and aural fullness (see Table 2) and for the associated vegetative symptoms (Fig. 3). However, no statistically significant difference between the two treatments was found.

All parameters of the vestibulospinal tests (recorded by CCG) distinctly improved during the course of therapy (see Table 3), with comparable results for both medications. Here, the distinct reduction of the parameter of "angular deviation" is of particular relevance, as it reflects an improvement of peripheral vertigo (e.g., rotatory vertigo), which is one of the key symptoms of the disease. The reduction of this parameter seems to reflect a normalization of a patient's condition, at least with respect to the balance system, and corresponds with the reduction of the S_M, chosen as the primary criterion of efficacy. Furthermore, the fixed combination was found to reduce the parameter of "lateral sway" in the Unterberger test, in a significantly stronger way than did betahistine, which may be attributed mainly to the centrally active component, dimenhydrinate, of the combination preparation.

Spontaneous or positional nystagmus was found in fewer than 10% of the patients, which parallels clinical experience. The majority of the Ménière's patients show spontaneous or provoked nystagmus during or immediately after the vertigo attacks but rarely during the period of remission [17]. Caloric responses are reduced in approximately 40–70% of the cases [2,17]; the excitability decreases more rapidly at the beginning of the disease and stabilizes in the following 10 years to one-half or one-third of the initial level [2,22]. In accordance with literature data [4], in the unilateral cases, the mean frequency at the affected side was approximately 30% lower than that at the nonaffected side and close to the lower limit of the normal range. Caloric nystagmus frequency remained largely unaffected by both treatments (Table 4).

In contrast to the patients' subjective assessment of hearing, pure-tone audiometry did not show a clear-cut

Table 4. Caloric Test (Electronystagmography) Results

Group of Patients Considered	ARL	Betahistine	*p* Value*
Per-protocol population	n = 40	n = 40	—
Before start of therapy	29.14 ± 7.91	28.66 ± 10.20	.675
Change from baseline after 12 weeks of therapy	−1.94 ± 5.60	−2.22 ± 7.95	.847
Unilateral disease	n = 26	n = 26	—
Affected ear			
Before start of therapy	24.77 ± 7.89	22.63 ± 6.32	.602
Change from baseline after 12 weeks of therapy	−0.48 ± 7.77	−1.65 ± 6.44	.707
Nonaffected ear			
Before start of therapy	32.81 ± 11.72	32.02 ± 12.96	.469
Change from baseline after 12 weeks of therapy	−3.10 ± 7.84	−2.58 ± 12.78	.498
Bilateral disease	n = 14	n = 14	—
Before start of therapy	29.79 ± 8.25	31.14 ± 12.91	.800
Change from baseline after 12 weeks of therapy	−2.21 ± 5.17	−2.41 ± 6.94	.818

ARL = Arlevert (cinnarizine-dimenhydrinate).
[a] Arlevert versus betahistine, Mann-Whitney U-test.
Note: Mean frequency of caloric nystagmus ± standard deviation (beats/30 sec) before therapy and mean change (decrease) ± standard deviation after 12 weeks of therapy.

Table 5. Audiometry Results

Group of Patients Considered	ARL	Betahistine	*p* Value[a]
Per-protocol population	n = 40	n = 40	—
Before start of therapy	32.22 ± 15.97	34.78 ± 16.03	.522
Change after 12 weeks	−1.86 ± 8.63	−0.77 ± 5.67	.506
Unilateral disease	n = 26	n = 26	—
Affected ear			
Before start of therapy	38.65 ± 16.97	47.31 ± 23.85	.275
Change after 12 weeks	−3.65 ± 8.78[b]	−1.25 ± 8.19	.509
Nonaffected ear			
Before start of therapy	13.65 ± 5.36	12.40 ± 2.80	.852
Change after 12 weeks	−0.48 ± 3.81	−1.01 ± 4.54	.595
Bilateral disease	n = 14	n = 14	—
Before start of therapy	43.48 ± 19.63	43.93 ± 18.41	.963
Change after 12 weeks	−1.47 ± 13.48	−1.96 ± 7.46	.783

ARL = Arlevert (cinnarizine-dimenhydrinate).
[a] Arlevert versus betahistine, Mann-Whitney U-test.
[b] Change from baseline significant at $p < .05$, Wilcoxon signed rank test.
Note: Mean hearing loss ± standard deviation (dB) before therapy and mean change (decrease) ± standard deviation after 12 weeks of therapy.

recovery of cochlear function during the treatment (Table 5). Hearing loss in Ménière's disease is sensory, and it characteristically displays a fluctuating but progressively worsening course, with little or no correlation to vestibular dysfunction [23,24]. The initial hearing loss of 40–45 dB at the affected ear is close to values found in the chronic phase of the disease [22,23,25] and compatible with the long mean duration of the disease (6 years) in the patient population of our study. Audiometry showed a slight but statistically significant recovery only in unilateral cases after 12 weeks of therapy with the combination preparation. The marked improvements in subjective judgment of hearing reported by both groups of patients during therapy might be attributed to a subjective increase in stimuli perception or processing within the context of general recovery.

The good antivertiginous efficacy of the combination preparation found in our study corresponds with the findings of previous clinical studies in patients suffering from vertigo of various origins [9,10], from which patients with Ménière's disease had been excluded. In patients with otogenic vertigo, acute vestibular disorders, and vertigo due to vertebrobasilar insufficiency, the fixed combination of cinnarizine and dimenhydrinate proved to be significantly more effective than was betahistine [10], whereas in Ménière's disease, our study demonstrates a very similar efficacy but no statistically significant difference between the two treatments.

The high efficacy of the two medications may be explained by their pharmacodynamic properties. From a pathogenetic point of view, Ménière's disease is the classic form of endolymphatic hydrops [24]. Several vasodilators have been used for the treatment of Ménière's disease, on the basis of the hypothesis that ischemia of the stria vascularis plays an important role in the development of endolymphatic hydrops [4]. Betahistine is known to cause vasodilatation and improvement of cochlear blood flow [26] through a complex interaction with histamine receptors (stimulation of H_1-receptors and inhibition of presynaptic H_3-receptors) [27]. The therapeutic efficacy of the fixed combination results from the different effects of its two active substances, cinnarizine and dimenhydrinate. The calcium antagonist cinnarizine leads to vasodilatation and improves circulation in compromised intra- and extracranial areas [14,28]. Furthermore, cinnarizine shows labyrinth sedative properties [28] and has therefore proven efficacy in the management of vertigo episodes of various origins, including also the acute phase of Ménière's disease. The actions of cinnarizine are reinforced by those of dimenhydrinate, which acts predominantly centrally. Dimenhydrinate exerts a regulating effect on the vestibular nuclei and closely associated vegetative centers in the brainstem [29,30]. Owing to its antivertiginous and antiemetic properties, dimenhydrinate is particularly effective in the treatment of vertigo and associated vegetative symptoms, and it is also recommended for the management of acute episodes in Ménière's disease [4,31].

The tolerability of both medications was judged by the vast majority of the patients (97.5%) as very good, which is underlined by a very low rate of dropouts (two patients in the betahistine group) and an absence of adverse events in any of the 80 patients who completed the study. This unusually low incidence of adverse events may reflect a generally positive attitude of the patients toward the study medication owing to the subjectively experienced success of the treatment, which may have prompted the patients to overlook minor inconveniences or adverse reactions.

In conclusion, the fixed combination of cinnarizine, 20 mg, and dimenhydrinate, 40 mg, proved to be safe and highly effective in the treatment of Ménière's disease. Owing to its pharmacological properties, the combination preparation may be used in both the management of acute episodes and in long-term therapy. Efficacy and safety were found to be similar to the widely used standard therapy with betahistine.

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