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Betahistine dihydrochloride in the treatment of peripheral vestibular vertigo

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Abstract The present study compares the efficacy and safety of betahistine dihydrochloride to that of a placebo in recurrent vertigo resulting from Meniere's disease (MD) or in paroxysmal positional vertigo (PPV) of probable vascular origin. The design was double-blind, multicentre and parallel-group randomised. Eleven Italian centres enrolled 144 patients: 75 of the patients were treated with betahistine (41 MD/34 PPV) and 69 with placebos (40 MD/29 PPV). The betahistine dosage was 16 mg twice per day for 3 months. Compared to the placebo, betahistine had a significant effect on the frequency, intensity and duration of vertigo attacks. Associated symptoms and the quality of life also were significantly improved by betahistine. Both the physician's judgement and the patient's opinion on the efficacy and acceptability of the treatment were in agreement as to the superiority of betahistine. The effective and safe profile of betahistine in the treatment of vertigo due to peripheral vestibular disorders was confirmed.

Keywords Betahistine · Meniere's disease · Paroxysmal positional vertigo

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Introduction

Betahistine is a drug indicated in the treatment of Meniere's disease and, more generally, of peripheral vertigo disorders of different origins [1, 2].

The mechanism of action in betahistine is based on its interaction with H_1 and H_3 receptors, which leads to the inhibition of the firing activity of the vestibular nuclei (H_3 receptor antagonism), the decrease of the resting discharge at the labyrinthine ampullar hair cells (H_3 antagonist and H_1 agonist action) and the increase of cochlear blood flow (H_3 pre-synaptic heteroreceptors antagonism) [3, 4, 5, 6, 7, 8, 9].

The therapeutic effect of betahistine, as well its safety, has been shown in many controlled clinical studies in vertigo patients [10, 11, 12, 13, 14, 15, 16].

The aim of this study was to verify the effectiveness and safety of betahistine in comparison to a placebo in recurrent vertigo related either to Meniere's disease or to positional paroxysmal vertigo of probable vascular origin in a parallel-type design.

Materials and methods

The trial was designed as a multicentre study that was controlled, double-blinded, used parallel groups and was randomised for a series of four patients; it was balanced among the centres. The operative procedures of the study followed the recommendations of the Helsinki Declaration of 1964 and its subsequent revisions.

Within Italy, 11 hospital and university ENT centres were involved in the study. Each of these was given a series of four patients to recruit. There was a total of at least 140 patients, who were stratified into groups having recurrent vertigo related to Meniere's disease (MD) and positional paroxysmal vertigo (PPV) of probable vascular origin. The diagnosis of probable or possible Meniere's disease was made according to AAOO-HNS criteria [17]; the diagnosis of paroxysmal positional vertigo was based on the presence of episodes of transient (s or min) attacks of rotational vertigo induced by sudden head movements without auditory symptoms and with induction of the typical vertical-rotatory transient positional nystagmus at the Dix-Hallpike maneuver [18].

The admission criteria were: being an out- or in-patient between 18 and 65 years old, having signed an informed written consent, the withdrawal of interfering concomitant therapies at least 7 days before the start of the study treatment, having normal laboratory-documented renal and hepatic function and cooperating by adhering to the scheduled procedure. Both males and females were included in the study. The exclusion criteria were: having concomitant infectious and definite cerebro-vascular diseases, having diseases that were not compatible with and were contraindicated by the treatment under study, having concomitant therapy with anti-vertigo drugs, taking drugs that act on cerebral circulation, antihistamines, calcium antagonists, antiaggregants, thiazide diuretics, corticosteroids and benzodiazepines, having any major medical or surgical condition likely to interfere with the absorption, distribution, metabolism or excretion of the drug used in the study or having a terminal disease.

The sample size was determined considering a control of vertigo attacks in about 40% of the patients with a placebo, as reported in the literature, and an improvement of 25% with the active treatment. With an α value of 0.05 and a β value of 0.2, the power of 80% could be reached with 70 patients per treatment group.

The following treatments were compared: taking 8 mg tablets of betahistine dihydrochloride (BE) or a placebo (PL); the tablets were indistinguishable by colour, weight and flavour. They were supplied in identical packages with a fantasy name to keep the blindness. The drug and placebo tablets were supplied by Grunenthal-Formenti, Milan, Italy. The dosage used was 16 mg (two tablets) twice a day, administered at 8 a.m. and 8 p.m. after meals for 3 months. The treatment was assigned to the patient according to the random list of the relevant diagnosis (MD or PPV).

Control visits for the efficacy evaluation were planned at the baseline and at 15, 30, 60 and 90 days after the start. The following laboratory tests were performed at the baseline and 3 months later: blood cell count, serum creatinine, serum glucose, AST/SGOT, ALT/SGPT, γ-GT, alkaline phosphatase, BUN, serum bilirubine, serum sodium, serum potassium and urine analysis.

The efficacy parameters recorded in each case report form, with information from diary cards that had been given to the patients, were the following:

1. the number of vertigo attacks per month;
2. the GISFaV self-rating scale [19] for the determination of the disturbance stage of vertigo using values of intensity (V), duration (D) and associated symptoms (N) scored respectively by a four-point scale (V: 0 =absent, 1= mild, 2= severe, 3= disabling), a five-point scale (D: 0= none, 1=<1 min, 2=<15 min, 3= some hours, 4=≥1 day) and a three-point scale (N: 0= absent, 1= nausea, 2= vomiting);
3. the Dizziness Handicap Inventory (DHI) rating scale [20] for the identification of the difficulties that patients encounter during the vertiginous disease;
4. the Dizziness Assessment Rating Scale (DARS) [19] for the evaluation of the severity of the symptoms.

At the end of the study, the investigators' and patients' overall judgements respectively on treatment efficacy and acceptance (five-point scale: 0= null, 1= poor, 2= moderate, 3= good, 4= very good) and the doctor's preparedness to treat the patient again with the same treatment were expressed.

The time of the onset of adverse events (ADR), type of effect, severity, dose taken, duration of treatment, action taken, outcome of the event and causal relationship according to the investigator were reported.

The efficacy assessment was analysed according to both the intention-to-treat (ITT) and per-protocol (PP) analyses.

Continuous variables were analysed by ANOVA, and multiple comparisons within and between groups and non-parametric measures were analysed by the Friedman, Kruskal-Wallis and χ^2 tests.

Table 1 Characteristics of the patients at baseline

Variable	Betahistine group	Placebo group
Number of patients	75	69
Diagnosis		
Meniere's disease	41	40
Positional paroxysmal vertigo	34	29
Sex		
M	33	27
F	42	42
Smokers	22	17
Age (years)	46.9±13.1	48.8±14.3[1]
Weight (kg)	67.7±11.7	70.2±14.4[2]
Arterial blood pressure systolic (mmHg)	128.5±12.7	128.7±13.5[3]
Arterial blood pressure diastolic (mmHg)	79.9±7.2	80.3±6.7[4]
Heart rate (beat/min)	72.2±9.4	71.6±7.7[5]
Disease duration (months)	31.6±55.0	32.5±67.3[6]
Disease-free interval in the last 12 months preceding the study (days)	28.9±44.4	31.9±66.1[7]
Rate of patients with concomitant pathologies (%)	20	13
Rate of patients with concomitant therapies (%)	25.3	15.9
Rate of patients with previous antivertigo treatments (%)	40.0	31.9

1 P=0.31, *2* P=0.20, *3* P=0.97, *4* P=0.66, *5* P=0.83, *6* P=0.90, *7* P=0.50

In the intention-to-treat analysis, all the randomised patients were considered who had taken at least one dose of the drug being studied, who had carried out at least one complete examination involving all the measurements specified in the protocol and who had not violated the protocol.

The trial started in January 1999 and was completed in June 2001. The 11 centres enrolled 144 patients, 81 (56.3%) suffering from Meniere's disease and 63 (43.7%) from positional paroxysmal vertigo; the patients were evenly distributed according to treatments and other vital characteristics (Table 1).

All efficacy variables were homogeneous among treatments at the baseline. However, some differences were detected between the MD and PPV groups, even if their distribution between treatments was homogeneous. Concomitant therapies were more frequent in PPV than in MD (31.7% vs. 16.0%, $P<0.03$); previous antivertigo treatments were more frequent in MD (48.1% vs. 20.6%, $P= 0.001$); the disease duration was longer in MD (47.7 months vs. 11.8, $P<0.0003$), and the interval free from vertigo was longer in MD (34.5 days vs. 25.2, $P<0.005$).

Fifteen patients (ten in the BE group and five in the PL group) were excluded from the PP analysis because of protocol violations such as interfering concomitant therapies (four in the BE group and three in the PL), not coming to the 2-month follow-up visit (three in the BE group and two 2 in the PL) and adverse events (three in the BE group).

Results

Efficacy

The results and tables refer to the ITT analysis. The significance shown by the ITT analysis was confirmed by the PP analysis. Both the disorders, MD and PPV, behave similarly within treatments.

Compared to the baseline rate, the number of monthly vertigo attacks was reduced with betahistine, both in MD (from 6.70±9.56 at baseline to 2.06±2.78 after 3 months of treatment) and in PPV (from 6.90±14.41 at baseline to 1.91±3.51 after 3 months of treatment); the statistical significance compared to the PL was detected from the 1st month of treatment ($P<0.05$ for MD and $P<0.02$ for PPV with the multiple-pair comparison test) (Fig. 1).

The intensity score of vertigo was more frequently improved in BE-treated patients than in the PL-treated group from the time of the 15-day visit ($P<0.02$), with no difference between MD and PPV (Fig. 2).

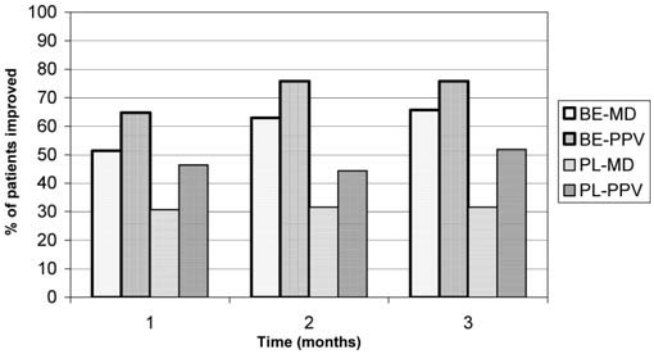

Fig. 2 Improvement in intensity score of vertigo during betahistine or placebo treatment (% of patients improved)

The number of patients with score improvement for the associated symptoms (tinnitus, fullness of the ear, nausea and vomiting) was significantly superior in the BE- versus the PL-treated patients from the 1st month up to the end of the study, with no difference in response between MD and PPV ($P<0.01$) (Fig. 3).

The duration of attacks was improved significantly more by BE than by the PL by the 2nd month ($P=0.007$). An improvement in the frequency of attacks became statistically significant in favour of betahistine at the 3-month visit, shifting to a monthly occurrence that was similar in MD and PPV, while remaining a weekly occurrence with the PL ($P=0.0008$). The quality of life showed a significantly different improvement between treatments starting from the 2nd month of the study ($P<0.02$ in favour of BE).

The overall GISFaV score, combining V, D and N values, presented a significant improvement trend compared to the baseline score in 70% of the patients in the betahistine group and in 30% of the placebo group ($P<0.0001$). Moreover, the patients' rates with all the GISFaV items equal to 0 at 3 months was 56.9% with betahistine and 3.1% with the placebo ($P<0.0001$).

Concerning the seven items in the Dizziness Assessment Rating Scale, six of them were improved by betahistine significantly more than by the placebo, with a signif-

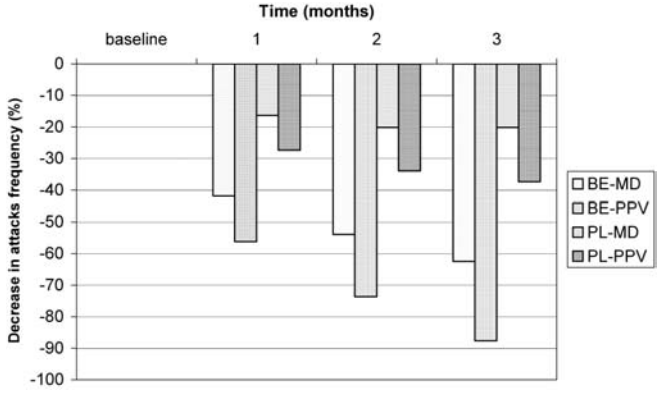

Fig. 1 Frequency of attacks during betahistine or placebo treatment (% decrease compared to the baseline)

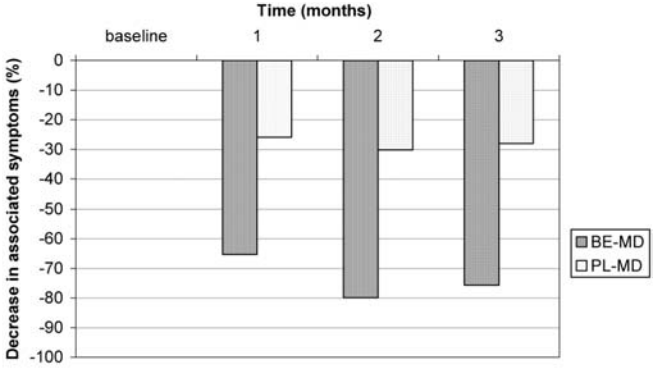

Fig. 3 Associated symptoms during betahistine or placebo treatment (% decrease compared to the baseline)

Table 2 Items of the dizziness assessment rating scale. (*MD* Meniere's disease, *PPV* positional paroxysmal vertigo, *NS* not statistically significant)

	Betahistine group		Placebo group	
	MD	PPV	MD	PPV
Standing imbalance (P=0.006)	–66.5%	–87%	–25.6%	–38.7%
Walking imbalance (P=0.07)	–65.4%	–89%	–41.3%	–35.0%
Vertigo feeling (P=0.016)	–65.2%	–92.7%	–10.7%	–38.5%
Vertigo intensity (P=0.01)	–63.8%	–86.0%	–23.3%	–53.5%
General impression of patient's dizziness given by the investigator (P=0.0004)	–72.7%	–82.0%	–29.9%	–55.9%
General impression of patient's dizziness given by the patient (P=0.0004)	–62.2%	–77.7%	–36.6%	–57.8%
Consciousness state	NS	NS	NS	NS

Table 3 Number and type of side effects. (*MD* Meniere's disease, *PPV* positional paroxysmal vertigo)

	Betahistine group		Placebo group	
	MD	PPV	MD	PPV
Headache	5	6	0	1
Dry mouth	0	1	0	0
Increased diuresis	1	0	0	0
Skin rash	1	0	0	0
Heart burn	1	1	1	1
Gastralgia	0	0	1	0
Drowsiness	1	0	0	0
Dysmielopoiesis	0	1	0	0
Abdominal pain	0	0	1	0
Extrasistoles	0	0	1	0
Oral formication	0	0	1	0

icant statistical interaction indicating a different trend in the two treatments for both MD and PPV. The state of consciousness was poorly present, and the variations are not clinically important (Table 2).

The overall DARS score was reduced by both treatments, and the trend to decrease was significantly in favour of betahistine: -80% BE (-66.7% in MD, -84.1% in PPV) vs. –35 PL (-31.2% in MD, -46.7% in PPV; $P<$ 0.00001). Moreover, the patient's rates with all the DARS items equal to 0 after 3 months of treatment was 53.8% with betahistine (42.4% in MD, 65.6% in PPV) and 14.1% with the placebo (15.8% in MD, 11.5% in PPV; $P<0.00001$).

For the Dizziness Handicap Inventory, the functional, physical and total severity scores were more significantly reduced with betahistine than with the placebo, with a significant statistical interaction, i.e., respectively, –65% (-45.7% in MD, -69.8% in PPV) vs. -30% (-26.0% in MD, -28.8% in PPV; $P=$ 0.0001), -60% (-41.3% in MD, -70.4 in PPV) vs. –30% (-19.4% in MD, -44.8% in PPV; $P<0.002$), and –65% (-40.2% in MD, -69.1 in PPV) vs. -35% (-28.1% in MD, -39.8% in PPV; $P<0.02$). The emotional score did not show any significant differences.

The physician's judgement of the efficacy of the treatment was good/very good in 73.5% of the patients in the betahistine group and 27.6% in the placebo group ($P<$ 0.00001), without differences between MD and PPV.

The doctor was prepared to treat the patient again with the same treatment in 86.8% of the BE group and in 36.9% of the PL group ($P<0.0001$).

The patients' opinions about the acceptability of the treatment was rated good/very good in 72.1% of the betahistine group and 30.8% of the placebo group ($P<$ 0.00001).

Safety

The blood pressure and heart rates did not show any statistically or clinically significant differences compared to the baseline rates during the study.

The rate of adverse events during the 3-month study period was similar in the two treatment groups: 21 patients out of 75 (28.0%) complained of adverse events with betahistine and 15 out of 69 (21.7%) with the placebo, with no statistical difference between MD and PPV (Table 3).

Discussion

The outcome of this study, which was double-blinded and placebo-controlled with parallel groups, confirms the efficacy of betahistine in the treatment of paroxysmal vertigo and Meniere's disease; this has already been observed both in crossover and parallel-group studies [10, 11, 12, 13, 14, 15, 16].

The two treatment groups were homogenous in their vital characteristics, distribution of diagnoses and efficacy variables at the start. The 3-month duration of the trial, even if planned as a short-term study, fulfils the recommendation for minimum length given by Schmidt and Huizing [2]. The data were analysed by both ITT and PP analysis, and both methods confirmed the significance found. The two diseases behave similarly within the treatments. Different tools were used to evaluate the effectiveness, and all were in full agreement at the end of the analysis.

Betahistine significantly reduced the number of vertigo attacks, their intensity score and their duration compared to the placebo both in MD and PPV. Furthermore, in MD the auditory-associated symptoms were significantly improved by betahistine. The significant improvement trend compared to the baseline of the placebo group is justified, because desire and expectation are salient determinants of the placebo effect.

Betahistine improved the patient's score on the Dizziness Assessment Rating Scale significantly more than the placebo for the evaluation of the severity of symptoms, such as the overall and specifically as the standing imbalance, feeling of vertigo, vertigo intensity and general impression of the patient's dizziness given by the investiga-

tor and by the patient. Also according to the Dizziness Handicap Inventory, betahistine induced a significantly larger reduction than the placebo in the functional, physical and total severity scores. The quality of life showed a statistically significant improvement in favour of the betahistine-treated patients. The physician's judgement on treatment efficacy and the patient's opinion on treatment acceptability were significantly in favour of betahistine, and this preference was confirmed by the preparedness of the doctor to treat the patient again with the same treatment in a remarkably different rate, i.e., about 87% for betahistine and 37% for the placebo.

In conclusion, the outcomes of this study are in agreement with the effective and safe profile of betahistine, as reported in other short-term or long-term trials, carried out with a similar methodology [10, 11, 12, 13, 14, 15, 16] and the statement on its efficacy in treating different forms of vertigo of peripheral vestibular origin, either as Meniere's disease or paroxysmal positional vertigo. According to the methodological suggestions of Schmidt and Huizing [2], Meniere's disease patients who had participated in the trial did not stop their medication at the end of the study. None of them had a significant worsening of the symptoms or had to undergo surgery or gentamycin treatment during the following 12 months.

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