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VESTIBOLOGY

Effect of a fixed combination of nimodipine and betahistine versus betahistine as monotherapy in the long-term treatment of Ménière's disease: a 10-year experience

Effetto della somministrazione combinata di nimodipina e betaistina nel trattamento a lungo termine della malattia di Ménière: analisi retrospettiva di 10 anni di esperienza clinica

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SUMMARY

Despite an abundance of long-term pharmacological treatments for recurrent vertigo attacks due to Ménière's disease, there is no general agreement on the their efficacy. We present the results of a retrospective study based on a 10-year experience with two long-term medical protocols prescribed to patients affected by Ménière's disease (diagnosed according to the American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium guidelines) who completed treatments in the period 1999-2009. A total of 113 medical records were analysed; 53 patients received betahistine-dihydrochloride at on-label dosage (32 mg die) for six months, and 60 patients were treated with the same regimen and nimodipine (40 mg die) as an add-therapy during the same period. Nimodipine, a 1,4-dihydropyridine that selectively blocks L-type voltage-sensitive calcium channels, has previously been tested as a monotherapy for recurrent vertigo of labyrinthine origin in a multinational, double-blind study with positive results. A moderate reduction of the impact of vertigo on quality of life (as assessed by the Dizziness Handicap Inventory) was obtained in patients after therapy with betahistine ($p < 0.05$), but a more significant effect was achieved in patients treated by combined therapy ($p < 0.005$). In the latter group, better control of vertigo was seen with a greater reduction of frequency of attacks ($p < 0.005$). Both protocols resulted in a significant improvement of static postural control, although a larger effect on body sway area in all tests was obtained by the fixed combination of drugs. In contrast, no beneficial effect on either tinnitus annoyance (as assessed by the Tinnitus Handicap Inventory) and hearing loss (pure-tone average at 0.5, 1, 2, 3 kHz frequencies of the affected ear) was recorded in patients treated with betahistine as monotherapy ($p > 0.05$), whereas the fixed combination of betahistine and nimodipine was associated with a significant reduction of tinnitus annoyance and improvement of hearing loss ($p < 0.005$). It was concluded that nimodipine represents not only a valid add-therapy for Ménière's disease, and that it may also exert a specific effect on inner ear disorders. Further studies to investigate this possibility are needed.

KEY WORDS: Vertigo • Hearing loss • Tinnitus • Hydrops • Calcium channel blockers

RIASSUNTO

Nonostante sia stata proposta una pletora di trattamenti farmacologici a lungo termine per ridurre la frequenza delle crisi di vertigine dovute alla malattia di Ménière, non esiste nella letteratura scientifica un consenso generale sulla loro efficacia. In questo studio retrospettivo vengono riportati i risultati di 10 anni di esperienza clinica relativa all'impiego di due protocolli farmacologici a lungo termine prescritti ai pazienti con diagnosi definitiva di malattia di Ménière (secondo i criteri dell'American Academy of Otolaryngology – Head and Neck Surgery Committee on Hearing and Equilibrium) che completarono il trattamento nel periodo 1999-2009. Sono state selezionate a questo scopo 113 cartelle cliniche; di queste, 53 relative a pazienti trattati con una somministrazione di betaistina-dicloridrato alla dose giornaliera di 32 mg per sei mesi mentre le altre 60 riguardavano pazienti trattati con una terapia addizionale di nimodipina alla dose giornaliera di 40 mg, per lo stesso periodo di tempo. La nimodipina, una 1,4 diidropiridina che blocca selettivamente i canali del calcio ad alto voltaggio di tipo L, era stata precedentemente testata come terapia monocomponente nelle vertigini ricorrenti di origine labirintica in uno studio multinazionale, in doppio-cieco riportando risultati positivi. Una moderata, seppure significativa, riduzione della percezione della disabilità relativa alla vertigine (valutata con l'impiego del Dizziness Handicap Inventory) è stata osservata nei pazienti trattati con betaistina ($p < 0,05$), ma un effetto maggiore è stato raggiunto nei pazienti trattati con l'associazione fissa dei due composti ($p < 0,005$). Con quest'ultima terapia, inoltre, si è ottenuto un controllo più efficace della vertigine ($p < 0,005$) in relazione alla frequenza degli attacchi. Entrambi i protocolli sono risultati in grado di migliorare significativamente il controllo posturale statico ma anche in questo caso un effetto più consistente è stato raggiunto dall'associazione dei due farmaci. La betaistina impiegata come monoterapia non ha avuto effetti significativi sul fastidio creato dal tinnito (valutato secondo il Tinnitus Handicap Inventory) nè tantomeno sulla perdita dell'udito (media aritmetica della soglia tonale per le frequenze di 0,5, 1, 2, 3 kHz nell'orecchio interessato) ($p > 0,05$). L'associazione di betaistina e nimodipina, all'opposto, ha determinato tanto una significativa riduzione del fastidio relativo alla presenza del tinnito quanto un miglioramento

dell'ipoacusia (p < 0,005). Pertanto è stato possibile concludere che la nimodipina rappresenta non solo una valida terapia aggiuntiva rispetto alla singola betaistina nel trattamento farmacologico a lungo termine della malattia di Ménière, ma che potrebbe di per sé esercitare un effetto positivo su diverse disfunzioni dell'orecchio interno, in particolare dell'organo del Corti. Ulteriori studi per approfondire tale ipotesi risultano comunque necessari.

PAROLE CHIAVE: *Vertigine • Perdita uditiva • Tinnito • Idrope • Calcio-antagonisti*

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Introduction

Pharmacological treatment of acute episodes in Ménière's disease (MD) does not usually represent a clinical problem since vestibular suppressants, including antihistamines such as promethazine, anticholinergic antiemetics like dimenhydrinate, and diazepam are almost always effective in reducing the most unpleasant symptoms namely vertigo, nausea and vomiting in a very short time [1]. Alternatively, infusion of diuretics appears to be somewhat useful even if their routine use should be adopted with caution because of dose-dependent, adverse side effects [2]. However, long-term pharmacological treatment aimed to reduce the frequency and intensity of vertigo attacks or even prevent flare-ups is a topic of general debate. First of all, even though it is generally accepted that MD is associated with endolymphatic hydrops (raised endolymph pressure in the membranous labyrinth of the inner ear), a definitive regimen for as long-term therapy remains elusive because the underlying aetiology of this condition is still not fully understood. Secondly, as pointed out by Jongkees in 1980 [3], MD spontaneously shows variably lengthy symptom-free periods, and therefore it is difficult to differentiate spontaneous remission from a therapeutic effect. Thirdly, studies adopted different designs, duration of treatment and drug dosages as well as methods to monitor outcomes so that results are rarely comparable. Finally, some studies included various peripheral vestibular diseases as cause of recurrent vertigo and results concerning MD alone cannot be extracted [4 5].

Nevertheless, some prevalent trends can be identified from the medical literature. For example, diuretics alone (acetazolamide) or in association with a low-salt diet are widely and routinely used, especially in the USA [6] and UK [7], although a recent review stated that their efficacy has not been demonstrated in adequate randomised, placebo-controlled studies [8]. Similar conclusions about betahistine, a structural analogue of histamine, were reported in a meta-analysis in 2001, revisited in 2011 [9], in contrast to other reviews which have concluded that its efficacy and safety are fully supported by modern evidence-based standards [10 11]. There is also an increasing interest for the effect of betahistine-dihydrochloride at dosages higher than those routinely used in the past (32 mg tid and lower), while the results of three recent open trials were controversial [12-14]. Calcium channel blockers, namely flunarizine, cinnarizine and nimodipine in the treatment of vertigo have been used for many years in Europe [15], and their efficacy and safety have been investigated in two double-blind studies that included different types of recurrent vestibular vertigo [16 17]. Only two pilot studies specifically investigated the beneficial use of nimodipine in the medical treatment of MD [18 19], and both reported encouraging results. Interestingly, there are few clinical trials about the use of combination of drugs in the treatment of MD [20] despite experimental evidence suggesting that multi-component therapeutics often are more successful than single component treatment [21].

Therefore, the aim of this work was to retrospectively analyze the results of 16 mg of betahistine-dihydrochloride taken twice a day (32 mg die) for six months as a single component therapy versus a fixed combination of 16 mg of betahistine-dihydrochloride taken twice a day (32 mg die) and 20 mg of nimodipine taken twice a day (40 mg die) for 6 months in patients with MD in the period from 1999-2009. The former long-term pharmacological treatment was the medical management of patients with definite MD, according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium diagnostic guidelines (Appendix 1) [22], prescribed by the first author from 1999 to 2003. Thereafter, the latter therapeutic protocol was used and is still employed with minor adjustments before adopting intratympanic gentamicin injection and/or ablative procedures if systemic pharmacological treatment results unsatisfactory.

Materials and methods

Selection of medical records

Of 6251 outpatients who attended the tertiary Centre for Vestibular Diseases and Rehabilitation of the University Hospital of Modena, Italy, in the period 1999-2009, 258 were diagnosed with definite MD. Criteria for medical records to be included were established in a preliminary session by three senior audiologists (M.D, G.E, P.L.). Cases to be included in the study were relative to patients affected by: (a) unilateral MD, diagnosed as definite; (b) functional level between 1 and 5; c) all MD patients should have completed medical treatments with no or minor adverse effects; d) all selected medical charts should include a complete history of patient, neurological and otologi-

cal examinations. Pure-tone audiometry, tympanometry, electronystagmography (including caloric tests), posturography and self-assessment questionnaires should be available at admittance and at the end of follow-up. Charts were completed by at least one magnetic resonance imaging to exclude the VIII nerve and cerebellar and brainstem lesions. Exclusion criteria were (a) previous or current professional exposure to noise and noise-induced hearing loss; (b) middle ear diseases; (c) previous ablative surgery procedures; (d) previous intratympanic gentamicin and/or corticosteroids injections; (e) other simultaneous treatments namely diuretics, corticosteroids, vasodilators and low-salt diet; (f) bilateral MD because other treatment modalities, including corticosteroids, were adopted; (g) functional level scale > 5 because of gentamicin intratympanic injection and/or vestibular neurectomy were directly prescribed to patients in such cases. Four younger coworkers (BMR, ACM, ACE and NV) who were blinded to the purpose of the study selected 113 medical records that met inclusion criteria. In 53 cases, MD patients had been treated with betahistine (group A), and in 60 cases with the fixed combination of betahistine and nimodipine (Group B). This study was approved by the Ethical Committee of the University Hospital of Modena in 2010 (ref. 102/6-010).

Efficacy outcome parameters

According to the AAO-HNS Committee on Hearing and Equilibrium guidelines for evaluation of therapy (appendix 1) control of vertigo was assessed by the formula (X/Y) x 100, where X is the average number of definitive spells per month for 6 months (from 18 to 24 months after therapy), and Y is the average number of definitive spells per months for the 6 months before therapy. The greater the number, the less efficacious the effect of treatment on the frequency of spells. These data were collected by routinely inviting MD patients to report their symptomatology in a standardized diary card. Furthermore, hearing function changes were assessed by comparison between the worst audiogram (four-tone average hearing threshold at 0.5, 1, 2 and 3 kHz in the affected ear) of each of the same two six-month intervals. Finally, stage of disease and functional levels were also determined in the aforementioned time intervals. These latter data were recorded during periodic check-up visits. These outcome parameters were chosen to follow the AAO-HNS Committee on Hearing and Equilibrium main guidelines for evaluation of therapies and allows comparison of the results of this study with those of other international experiences [23].

Further outcome measures

In accordance to the standardized diagnostic protocol of the Centre for Vestibular Disease and Rehabilitation of the University Hospital of Modena, the total scores of two self-administrated psychometric questionnaires regarding perceived dizziness disability (Dizziness Handicap Inventory) [24] and tinnitus annoyance (Tinnitus Handicap Inventory) [25] before therapy and at the end of follow-up were also considered. The Dizziness Handicap Inventory is a 25-item questionnaire internationally adopted to appreciate the multidimensional impact of vertigo on self-perceived disability. A "yes" response gives a score of 4 points, "sometimes" 2 points, and "no" 0 points. The total score ranges from zero (no disability) to 100 (severe disability). The Tinnitus Handicap Inventory is a 25-item questionnaire designed to assess the severity of tinnitus annoyance. Each item has 3 potential answers with "yes" assigned 4 points, "sometimes" 2 points, and "no" 0 points. This leads to a total score ranging from 0 indicating no tinnitus handicap and 100 the worst annoyance. The Italian versions of both DHI and THI have been demonstrated to maintain the same validity as the original ones [26 27]. Posturographic data were also taken into consideration, and were obtained using a stable force-plate sensitive to vertical forces (S.Ve.P, Amplifon). Patients were requested to maintain a relaxed, motionless upright stance, stand bare foot with feet at an angle of 30°, with a natural head-neck posture, under 4 different conditions: 1) gazing at a steady, vertical light bar at a distance of 150 cm (EO), 2) with eyes closed in total darkness (EC), 3-4) facing the wall in front on which a digital projector offered a full-field linear optokinetic stimulation represented by vertical alternating dark and light stripes 30 cm in diameter, delivered at a speed of 30°/sec, in the horizontal plane. The optokinetic visual stimulation was firstly delivered toward the normal labyrinth (OKS-NL) and then towards the affected one (OKS-AL). These two trails were specifically designed to test postural reaction to visual-vestibular conflicting environmental conditions, which are known to be critical for patients with an uncompensated vestibular lesion [28 29]. The duration of each test was 52.2 sec and the analysis frequency of signal was 5 Hz. The body sway path was computed by detecting the body's centre of pressure and calculating an elliptic area, which corresponds to 90% of its position over time and expressed in mm. This procedure was designed to eliminate 10% of the more extreme positions that could be due to involuntary perturbations of quiet stance.

Statistical analyses

As a preliminary statistical analysis, the Student's independent t-test was used to compare the age of patients before treatment. A chi-square (χ^2) procedure was performed to test the null hypothesis that MD patients were not differently distributed in the two selected samples before treatment with respect to gender, stage of disease, functional level and presence of tinnitus. The same statistical procedure was adopted to analyze the distribution of patients with respect to functional level and stage of disease at the end of follow-up. Finally, the χ^2 procedure

Table I. Distribution of patients with definite MD in Group A and B considering gender, stage of disease and functional level before medical treatment. Pearson's chi-square values, df and asymptotic significance are reported (percentages in brackets).

	Group A (n = 53)			Group B (n = 60)			χ^2		
Gender	**Males**		**Females**	**Males**		**Females**	**Value**	**df**	**Asympt Sig.**
	21 (40)		32 (60)	19 (32)		41 (68)	0.799	1	0.246
Stage	2	3	4	2	3	4			
	8 (15)	37 (70)	8 (15)	3 (5)	46 (77)	11 (18)	3.301	2	0.192
Functional Level	3	4	5	3	4	5			
	8 (15)	42 (79)	3 (6)	4 (7)	50 (83)	6 (10)	2.605	2	0.272

** Asymptotic significance p < 0.05; † asymptotic significance p < 0.005.*

Table II. Distribution of patients with definite MD considering stage of disease and functional level after follow-up. Pearson's chi-square values, df and asymptotic significance are reported (percentages in brackets).

Stage		**Group A (n = 53)**				**Group B (n = 60)**					χ^2		
											Value	**df**	**Asympt Sig.**
1	**2**	**3**	**4**		**1**	**2**	**3**	**4**					
3 (6)	14 (26)	19 (36)	17 (32)		6 (10)	19 (32)	29 (48)	6 (10)			8.7	3	0.034*
Functional Level													
1	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**				
4 (8)	16 (30)	7 (13)	22 (41)	4 (8)	6 (10)	36 (61)	11 (18)	5 (8)	2 (3)		19.9	4	0.001†

** Asymptotic significance p < 0.05; † asymptotic significance p < 0.005.*

Table III. Mean values and standard deviations of PTA, THI and DHI scores before therapy and at the end of follow-up in Groups A (treatment = betahistine) and B (treatment: betahistine and nimodipine) and paired t-test values.

Group A	**Before therapy**		**After therapy**		**Paired T-test**		
	Mean	**SD**	**Mean**	**SD**	**t**	**df**	**p**
PTA (affected ear)	54.1	12.6	52.3	19.6	1.03	52	0.307
DHI (total score)	50.1	11.7	46.4	13.7	2.6	52	0.012*
THI (total score)	28.5	23.4	28.9	21.8	-0.26	52	0.796
Group B							
PTA (affected ear)	56.4	10.5	47.3	16.8	4.9	59	< 0.001†
DHI (total score)	52.3	11.4	44.8	17.5	3.5	59	< 0.001†
THI (total score)	27.8	14.7	23.7	12.0	4.2	59	< 0.001†

** p < 0.05; † p < 0.005.*

Table IV. Mean values, standard deviations and paired t-tests of body sway path in eye open (EO), eye closed (EC), during full-field horizontal stimulation towards the affected ear (OKS-AL) and to the normal one (OKS-NL)before therapy and at the end of follow-up in Groups A (treatment = betahistine) and B (treatment = betahistine and nimodipine).

Group A	**Before therapy**		**After therapy**		**Paired T-test**		
Sway path	**Mean**	**SD**	**Mean**	**SD**	**t**	**df**	**p**
EO	358.8	274.5	321.6	335.2	0.6	52	0.547
EC	575.4	261.1	458.0	202.9	2.4	52	0.023*
OKS-AL	483.9	296.9	442.1	281.9	2.5	52	0.014*
OKS-NL	373.3	293.8	320.9	157.4	1.4	52	0.151
Group B							
EO	320.8	303.6	167.2	128.4	3.5	59	0.001†
EC	494.1	207.6	368.6	146.8	3.5	59	0.001†
OKS-AL	443.7	335.5	317.6	121.0	3.3	59	0.002†
OKS-NL	327.7	291.8	186.4	137.1	2.4	59	0.006*

** p < 0.05; † p < 0.005.*

was employed to verify the null hypothesis that the distribution of MD patients who reported unsatisfactory control of vertigo, and were hence submitted to intratympanic gentamicin injections was not different in the two samples. The paired T-test was performed to compare PTA of the affected ear (the worst audiogram available before admittance to therapy and in the follow-up period after treatment), DHI and THI scores, body sway path in EO, EC, OKS-NL and OKS-AL before treatment and at the end of follow-up. Independent-T test was again adopted to compare control of vertigo in the two groups. The SPSS package (version 16.0 SPSS Inc., Chicago, Illinois, US)

was used, and statistical significance level was set at $p < 0.05$ in all procedures.

Results

Mean age did not differ significantly between patients in group A (mean = 45.3, SD = 6.7) and B (mean = 43.9 SD = 7.3) (t = 1.04, df = 111, p = 0.299). Patients with MD were not differently distributed in the two groups considering gender ($\chi^2 > 0.05$), stage of disease ($\chi^2 > 0.05$) and functional level before therapy ($\chi^2 > 0.05$) (Table I). Tinnitus was present in 46 patients in Group A (87%) and in 47 patients in Group B (78%) (Pearson's value = 1.4, df = 1, $\chi^2 = 0.240$). It could be noted that no MD patients with stage 1 and/or functional level below 3 were present; one explanation is that both possible and probable MD were not included, and that patients with initial and mild symptomatology are not usually referred to the tertiary Centre for Vestibular Diseases and Rehabilitation. Another explanation is that only patients with definite MD were enrolled in this retrospective analysis and probably which led to the exclusion of patients with uncertain diagnosis and/or mild hearing and vestibular dysfunctions. As seen in Table II, significant changes in the distribution of MD patients of the two groups were seen in the follow-up period. In particular, the percentages of MD patients in group B belonging to the 1th, 2nd and 3th stages were higher than those in Group A and lower for the 4th and 5th stages ($\chi^2 < 0.05$). Moreover, PTA in patients in Group A did not show any significant improvement in the interval between the 6 months before treatment and the 6 months of follow-up after one year from the end of therapy ($p > 0.05$) (Table III). In contrast, a significant amelioration of PTA in Group B was observed in the follow-up period compared to the period before treatment ($p < 0.005$) (Table III). Taken together, these results suggest a better therapeutic effect of the fixed combination of betahistine and nimodipine on hearing acuity than betahistine alone.
At follow-up, the percentages of patients in group B were significantly higher than those in group A considering the functional levels from 1 to 3 and lower for the 4th and 5th ($\chi^2 < 0.005$), thus suggesting a greater beneficial effect of the fixed combination of compounds on the impact of vertigo on daily activities (Table III). This result is corroborated by the observation that MD patients treated with the fixed association of betahistine and nimodipine showed a better control of vertigo at the end of the follow-up (mean =13.3, SD = 25.3) than MD patients who were treated with betahistine alone (30.7, SD = 30.8) (Independent t-test: t = 3.3, df =111, p = 0.001) (Fig. 1). It should be observed that large values of standard deviation for both groups clearly suggest a great inter-individual variability to both therapeutic modalities. MD patients in Group A did not report any decrease in tinnitus annoyance between admittance to therapy and the end of follow-up ($p > 0.05$) (Table III). However, the perception of dizziness handicap as assessed by DHI was moderately reduced in the same interval ($p < 0.05$) (Table III). A highly significant reduction of tinnitus annoyance ($p < 0.005$) as measured by the THI score in the interval between admittance to therapy (mean = 27.8) and the end of follow-up (mean = 23.7) was observed in MD patients of group B (Table III). These patients also reported a more significant reduction ($p < 0.005$) of perceived dizziness handicap as expressed by DHI score at the end of follow-up compared to the period before treatment than those in group A (Table III). As seen in Table IV, the total amount of body sway path of group A patients in EO and OKS-NL conditions did not significantly vary ($p > 0.05$); however, a moderate but significant decrease of body sway path was present at the end of follow-up in EC and OKS-AL conditions ($p < 0.05$). More remarkable reductions of body sway area were recorded in group B; body sway path was greatly reduced in EO, EC and OKS-AL conditions ($p < 0.005$) and a moderate but significant decrease was observed in OKS-NL condition ($p < 0.05$) (Table IV). Since 13 patients in Group A (24.5%) and 4 (6.7%) in Group B continued to experience frequent relapses of vertigo after the end of follow-up, a total of 17 patients (15%) were submitted to intratympanic gentamicin instillation. The distribution of these patients with unsuccessful medical results was not similar in the two groups; the number of MD patients in group A that underwent intratympanic gentamicin injection was significantly greater than that in group B (Pearson's $\chi^2 = 7.1$, df = 1, asymptotic significance = 0.008).

Discussion

Betahistine, a structural analogue of histamine with weak histamine H(1) receptor agonist and more potent H(3) receptor antagonist properties, has been demonstrated to improve vestibular compensation in animal mod-

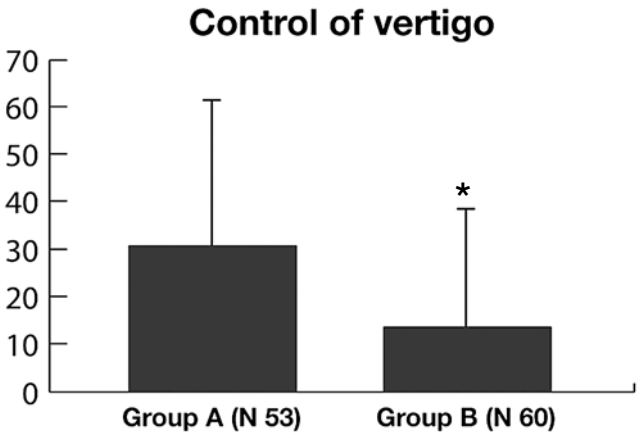

Fig. 1. Effect of betahistine-dihydrochloride at an on-label dosage of 32 mg/bid (Group A) vs a fixed combination of betahistine-dihydrochloride at the same dosage and nimodipine (40 mg/bid) as an add-on, off-label therapy (Group B) on control of vertigo in 113 MD patients (* = $p < 0.005$).

els of unilateral failure of vestibular function by different mechanisms [30]. In the central nervous system, it improves histamine synthesis within the posterior hypothalamus and enhances histamine release within vestibular nuclei through antagonism of H(3) heteroreceptors. The action of histamine on the vestibular nuclear cells on the affected side is considered the key mechanism that produces a rebalancing of neuronal activity between the two sides to promote recovery. In the inner ear of guinea pigs, betahistine increases blood flow by antagonizing local H(3) receptors resulting in an increased blood flow both in the posterior semicircular canal ampulla [31] and cochlear vessels [32]. A better perfusion of the inner ear vasculature has been presumed to be the basic mechanism by which betahisthine can potentially ameliorate inner ear vascular disorders that animal investigations have suggested to occur in the chronic hydropic ear [33]. Moreover, the perilymphatic administration of betahistine could greatly reduce the resting discharge of the ampullar receptor in the frog semicircular canal, postulating its possible inhibitory effects on the abnormal activity of the sensory hair cells induced by hydrops [34]. Moreover, in humans betahistine hydrochloride acts as a potent cerebral and peripheral microcirculatory vasodilator both in normal subjects [35] and in patients affected by cerebrovascular disease [36] when given orally. It is also known to facilitate vestibular compensation in patients with disabling MD after vestibular neurectomy by rapidly reducing the asymmetry of the vestibulo-ocular reflex (VOR) [37]. Disappointingly, experimental results of drugs on VOR are extremely rare in humans [38]; nonetheless, it has been clearly demonstrated that betahistine can differently affect VOR dynamics, namely velocity gain and duration of nystagmus, depending on the frequency of stimulation that is probably due to a specific activity on neurotransmission within the vestibular nuclei [39]. The possibility that betahistine can act as a neurotransmitter or a neuromodulator at peripheral vestibular end organs in humans is more controversial primarily because it has been observed that astemizole, an H(1) receptor antagonist that does not penetrate the blood-brain barrier, suppresses nystagmus in patients with chronic dizziness [40]. From this point of view, it seems a contradiction to treat patients with a structural analogue of histamine for a symptom that is also relieved by systemic antihistamines [41].

Nevertheless, the results of this study corroborate the most recent advances regarding the efficacy of betahistine in the long-term medical treatment of MD as on-label administration (32 mg die). In fact, it has been confirmed that it reduces the frequency of vertigo attacks [12 13] and improves quality of life through a significant reduction of perceived dizziness handicap in MD patients as well as in patients with various types of recurrent vertigo [5 42]. This study also focused on the efficacy of betahistine on the asymmetry of vestibulo-spinal reflexes, which appears to be one of the less frequently investigated aspect of MD; stabilometric data has shown that postural control is moderately improved by this treatment both in visual deprivation and in visual-vestibular mismatch conditions. Therefore, it supports a previous observation about its efficacy in the reduction of vestibulo-spinal reflex impairment and unsteadiness that occur in MD patients after vestibular neurectomy [43].

It is also been suggested that tinnitus annoyance and hearing loss due to MD are far less amenable to treatment with betahistine [9 44 45] since both THI total score and pure tone hearing threshold did not significantly improve.

Nimodipine, a 1,4 dihydropyridine that selectively blocks L-type voltage-sensitive calcium channels, is now considered to be a safe and well-documented drug for reduction of the severity of neurologic deficits resulting from vasospasm in subarachnoid haemorrhage [46]. The mechanism of nimodipine beneficial effect in such patients is not completely elucidated. It has both a preferential cerebral vasodilator action and a direct effect involving prevention of calcium overload in neurons, responsible of cellular damages, by a blocking action on L-type voltage-sensitive calcium channels. Administration of nimodipine induces an increase in plasma adenosine levels, a well-known vasodilatatory compound with a short biological half-life on brain circulation in humans [47]. There is also evidence that nimodipine may have a neuroprotective effect against ischaemia by entering into the cell and inhibiting excessive calcium ion influx in the mitochondria [48]. Increased fibrinolytic activity has been observed in patients with aneurysmal subarachnoid haemorrhage following treatment with nimodipine. This is considered to be due to a nimodipine-induced decrease in the level of plasminogen activator inhibitor [49 50]. This data suggests that nimodipine may act as an analogue of tissue-type plasminogen activator whose role is well-established in the treatment of sudden and chronic sensorineural hearing loss [51]. The off-label use of nimodipine in the treatment of peripheral vestibular disorders is supported by several lines of experimental data, and for example, there is good evidence for calcium channels at the periphery of the vestibular system that are predominantly the L-type [52]. The effect of several calcium channel agonists and antagonists on the whole nerve firing rate in an isolated frog semicircular canal preparation have been studied [53]. Even if resting activity was affected by all dihydropyridines tested, only nimodipine was able to reduce the mechanically-evoked activity. This suggests that nimodipine might potentially reduce spontaneous nystagmus due to an abnormal resting discharge of vestibular hair cells induced by an increased pressure of the endolymph [54].

In brainstem, neurons in the medial vestibular nucleus show adaptive changes in firing rate responses that are correlated with VOR gain (the ratio of evoked eye ve-

locity to input head velocity). Moreover, neurons of the vestibular medial nuclei express L, T and N-type calcium channels [55]. Thus, calcium-channel blockers can differently affect VOR depending on the functional role of the subtypes of channel in each synapse. In fact, the firing rate response of neurons in the medial vestibular nuclei is reduced by increasing extracellular calcium and increased either by lowering extracellular calcium or with antagonists to calcium-dependent potassium channels and N- and T-type calcium channels [56]. When tested in elderly patients with chronic cerebrovascular disorders, nimodipine appears to enhance learning and memory [57] that are cognitive functions whose role is crucial during vestibular compensation process [58]. Finally, since nimodipine has been used as prophylaxis for migraine, it is possible that it also exerts a beneficial effect on the course of MD as for other antimigrainous drugs [59] even if the underlying mechanism remains to be elucidated.

L-type calcium channels have been described in the peripheral auditory systems of different species, and it has been shown that they primarily mediate neurotransmitter release from hair cells [60]. Diffusion of nimodipine into the scala tympani of the cochlea significantly elevated threshold, decreased the amplitude and increased the latency of the action potential in a reversible manner [61]. Moreover, it has been shown that the mobility of the outer hair cells in the organ of Corti is inhibited by the presence of nimodipine suggesting its protective role compared to their abnormal mechanical stimulation due to the hydropic pressure on the cochlear structures [62]. In fact, the results of this study clearly demonstrate the beneficial effect of nimodipine as an add-on therapy in definite MD because its fixed combination with betahistine resulted in a more efficient control of vertigo spells, greater amelioration of perceived dizziness handicap and better control of static posture in all visual conditions than betahistine as a single component therapy. Despite these observations, which clearly indicate an additional beneficial effect of nimodipine in the treatment of MD, no conclusion about its own interaction with the vestibular system in humans is actually definitive. Nimodipine appears to exert a specific effect on the auditory system since its use was associated with reduction of tinnitus annoyance and improvement of pure-tone hearing threshold. These data partially confirm previous experimental evidence in an animal behavioural model [63] and clinical experience in humans [64]. It therefore seems reasonable to accept the beneficial action of nimodipine on cochlear dysfunction on the basis of its well-documented effect on hair cell calcium channels whose dysfunction could play a dominant role in those inner ear disorders that can be referred to as "channelopathy [65]. These results have at least two clinical implications; firstly, the question if the off-label prescription of nimodipine alone could be effective in MD, and secondly if its use should be extended to other types of inner ear dysfunctions and central vestibular disorders. Finally, it should be noted that no single or multicomponent medical treatment is associated to optimal control of vertigo in all patients with definite MD, so that intratympanic gentamycin injection or ablative procedures are adopted in cases that are refractory to long-term medical treatments.

Conclusions

Betahistine has been prescribed to patients with MD for many years in Europe, and recent reviews suggest that it is both effective and safe in adequate double-blind, controlled studies. As also suggested by this retrospective study, its efficacy is limited to control of vertigo spells. Disappointingly, no therapeutic effect of betahistine on tinnitus and hearing loss due to MD emerges from either the international medical literature or the results of this study. Nonetheless, this retrospective study confirms recent clinical experience about its efficacy in reduction of postural symptoms due to the asymmetry of vestibulo-spinal reflexes. Nimodipine exerts not only an additional effect on the control of vertigo attacks and a further reduction of vestibulo-spinal impairment, but also a specific and positive action on tinnitus annoyance and sensorineural hearing loss. Therefore, the fixed combination of betahistine and nimodipine seems to provide patients with MD the typical advantage of a multicomponent therapy, namely a better control extended to the majority of symptoms. Further investigations with adequate study design on the off-label prescription of nimodipine alone in inner ear dysfunctions in humans are recommended.

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Appendix 1

American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) Committee on Hearing and Equilibrium diagnostic guidelines (1995)

Source
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Diagnosis of Meniere's Disease

Possible Meniere's disease

- Episodic vertigo of the Meniere's type without documented hearing loss, or sensorineural hearing loss, fluctuating or fixed, with dysequilibrium but without definitive episodes
- Other causes excluded

Probable Meniere's disease

- One definitive episode of vertigo
- Audiometrically documented hearing loss on at least one occasion
- Tinnitus or aural fullness in the treated ear
- Other causes excluded

Definite Meniere's disease

- Two or more definitive spontaneous episodes of vertigo 20 min or longer
- Audiometrically documented hearing loss on at least one occasion
- Tinnitus or aural fullness in the affected ear
- Other cases excluded

Certain Meniere's disease

- Definite Meniere's disease, plus histopathologic confirmation

Stage of disease

Staging of Meniere's disease proposed by AAO-HNS (1995) is based on the arithmetic mean of the pure tone thresholds at 0.5, 1, 2, and 3 kHz of the affected ear, using the worst audiogram during the interval 6 months before treatment. Accordingly, stage I means four-tone average less than 26 dB; stage II, 26-40 dB, stage III, 41-70 dB, and stage IV, more than 70 dB

Stage	Four-tones average (0.5, 1, 2, 3 kHz) (dB)
1	< 26
2	26-40
3	41-70
4	> 70

Functional level scale (FLS)

According to AAO-HNS (1995) regarding the current state of overall function, not just functioning during attacks.

FLS	Patient's subjective experience
1	My dizziness has no effects on my activities at all
2	When I am dizzy, I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.
3	When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness
4	I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.

5	I am unable to work, drive, or take care of my family. I am unable to do most of the active things that I used to do. Even essential activities must be limited. I am disabled.
6	I have been disabled for one year or longer and/or I receive compensation (money) because of my dizziness or balance problem

Control of vertigo

Stated that the frequency of definitive attacks of vertigo for the period six months before treatment should be compared with the frequency of attacks occurring in the interval 18 to 24 months after treatment and the formula to be applied is (X/Y) x 100 rounded to the nearest whole number. X is the average number of definitive spells per months for the 6 months 18 to 24 months after treatment and Y the average number of crisis per month for the 6 months before. The greater the numerical expression, the worse the control of vertigo attacks after therapy.

Control of vertigo	Numerical value
A	0 (complete control)
B	1-40
C	41-80
D	81-120
E	> 120
F	Secondary treatment initiated due to disability of vertigo