**Vestibology**

**Association of cinnarizine and betahistine in prophylactic therapy for Ménière’s disease with and without migraine**

L’associazione di betaistina e cinnarizina nella profilassi degli episodi vertiginosi nella Sindrome di Ménière con e senza comorbidità emicranica

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**Summary**

Prophylactic therapy of Ménière’s disease (MD) includes betahistine and calcium-blockers (the latter also useful for migraine prevention). The aim of our work was to assess the efficacy of combined therapy with cinnarizine and betahistine in MD subjects both with and without migraine and poorly responsive to betahistine alone. Fifty-two MD subjects were included who were poorly responsive to betahistine during 6 months of follow-up; 29 were migraineurs. Combined therapy was administered with betahistine 48 mg/day and cinnarizine 20 mg BiD for 1 month, 20 mg/day for 2 weeks and 20 mg every 2 days for 2 more weeks, and then repeated. Results were collected over 6 months of follow-up. MD subjects with and without migraine demonstrated a decrease in both vertigo spells and migrainous attacks during combined therapy (from 9.4 to 3.8 and from 6.8 to 5.9 in 6 months, respectively, for vertigo spells, while migraine decreased from 3.8 to 1 in 6 months, respectively). A correlation was seen between decrease of vertigo spells and headaches in the sample of MD subjects with migraine. Our data support a proactive role for cinnarizine in preventing vertigo spells, especially in MD patients with migraine.

**Key words:** Ménière’s Disease • Migraine • Therapy • Betahistine • Calcium-Blockers • Cinnarizine

**Introduction**

Ménière’s disease is an inner ear disorder characterised by recurrent episodes of vertigo, hearing loss, fullness and tinnitus. Increased endolymphatic pressure is commonly accepted as the pathogenetic mechanism¹, although according to some authors hydrops may be the consequence of a primitive damage of the inner ear².

Criteria for the diagnosis of definite MD, established in 1995 by the AAO-HNS, are mainly based on phenotype of episodic vertigo, consisting in the presence of at least two episodes of vertigo of at least 20 min, audiometrically confirmed sensorineural hearing loss on at least one occasion, tinnitus or aural fullness during episodes and exclusion of other possible causes of vertigo³. Demonstrated
hearing loss in the vertigo-free period is not required for the diagnosis of definite MD.
Migraine is a neurological disorder characterised by episodic headaches of pulsatile quality, often associated with phonophobia and photophobia, with a prevalence of 15-17% in women and 5-8% in men.
Epidemiological studies have shown an association between MD and migraine, variously reported between 43% and 56% and described by Prosper Ménière himself. The high frequency of migraine in MD population may underline a pathophysiological link between the two disorders. Recent papers have focused on increasing evidence that migraine per se may provoke episodic vertigo, and clinical entity is defined as vestibular migraine (VM).
Among other symptoms, diagnosis of MD relies more on audiometric findings, even though fluctuation of hearing level has also been reported in patients with VM. In some cases, at the initial stages of episodic vertigo, differential diagnosis between MD and VM may be a puzzling dilemma.
Betahistine has been demonstrated to be useful in prevention of episodic vertigo in MD, while calcium-blockers are among the most widely used drugs in prophylactic therapy of migraine. Cinnarizine has also been studied as monotherapy for MD, but demonstrated a lower efficacy compared to betahistine in preventing vertigo spells in a sample of 36 MD subjects. A recent report focused on the possibility that nimodipine may increase efficacy of betahistine in prevention of vertigo spells in MD patients.
The aim of our investigation was to confirm the efficacy of combined prophylactic therapy with calcium-blocker and betahistine in MD subjects with and without comorbidity for migraine, and to establish a possible correlation between reduction of both headache and vertigo spells in MD subjects with migraine.

Materials and methods
In our study we included 29 patients affected by definite Ménière’s Disease according to AAO-NHS criteria also presenting a diagnosis of migraine according to IHS criteria and 23 patients with MD but without migraine. They were recruited among outpatients who attended the Centre for vestibular disorders at San Raffaele hospital in Milan and Policlinico San Matteo in Pavia between January 2010 and July 2011.
They were consecutively recruited if they completed 6 months’ follow-up among patients poorly responsive to mono-therapy with betahistine 48 mg/day during the first 6 months. During the next 6 months, they underwent combined therapy with betahistine 24 mg BID and cinnarizine 20 mg BID for 1 month, then 20 mg/day for 2 weeks and 20 mg every 2 days for 2 further weeks; successively, they restarted cinnarizine 40 mg/day.
Exclusion criteria were current exposition to noise, a middle ear disorder or previous intratympanic therapies with gentamycin or steroids. During the 12 months of the study, no further therapies for MD or migraine (e.g. diuretics, steroids, antiepileptics) or drugs active on the central nervous system (benzodiazepines and selective serotonin reuptake inhibitors) were given. However, dietary measures were suggested in all patients, especially increased fluids and reduced salt intake.
Clinical history included the presence of a familial history of vertigo and an autoantibody screening (anti-nucleum, smooth muscle, thyroid, cardiolipin, lupus-like anticoagulant and β2-glycoprotein). In our sample, 4 patients referred a familial history of vertigo. In the group of patients with migraine, 11 of 29 (38%) presented positivity for at least one of the autoantibodies (in 7 anti-thyroids), including 5 of 23 among those without migraine (22.7%). Mean age at inclusion of the sample of migraineurs was 48.8 ± 9.6 years and 22 were females, while non-migraineurs presented with a mean age of 49.2 ± 7.6. No statistical difference was detected between the two groups.
The first attack of vertigo was noted at 36.9 ± 7.8 years of age in the sample of migraineurs and 40.9 ± 10.4 among non-migraineurs, with the first headache at the age of 28.9 ± 5.5 years. Headache preceded the occurrence of vertigo in all subjects except one, in which they occurred in the same year. Ten patients referred that a vertiginous attack was followed by headache in at least two cases.
Audiometric values were saved at the beginning of combined therapy and the 12 month control, and the mean value of pure tone audiometry (PTA) at 500, 1000, 2000 and 3000 Hz at the beginning and at the end of combined therapy was calculated.
Main outcome was considered the number of spells during the 6 months before combined therapy and the following 6 months. According to AAO-HNS guidelines, efficacy was evaluated with the formula (x/y) x 100, where x is the average number of vertigo spells per month in the 6 months of combined therapy, and y the average number of spells per month in the 6 months of previous monotherapy. The same formula was used to assess efficacy of therapy in controlling headaches. The lower the number, the more beneficial the therapy.

Statistical analyses
The significance of any difference in continuously distributed variables between the two groups was examined by t-test for independent samples. Significance of non-normal distributed values was assessed with a Mann-Whitney test. The chi-square test was used to assess differences for nominal values. Correlations were assessed with a Spearman test.

Results
Results and statistics of MD patients with migraine are
Prophylaxis of Ménière’s disease with betahistine and cinnarizine

A summary of the results in the sample of subjects with MD without migraine is presented in Table I, while Table II shows the results in the sample of subjects with MD without migraine. Among migraineurs, the value of the formula \( (x/y) \times 100 \) for vertigo spells was lower than 50% in 13 cases, in the range between 50-75% in 3 more cases, while in 13 cases therapy demonstrated no efficacy. In this sample, seven of 11 subjects with positivity for autoantibodies, and 6 of 18 without positivity, presented a value lower than 50 (\( p = 0.1 \)).

The value of the formula \( (x/y) \times 100 \) for headache attacks was below 50% in 17 cases, in the range between 50-75% in 2 cases and over 75% in 10 cases. Nine of eleven subjects with positive autoantibodies and 8 of 18 remaining subjects presented a value lower than 50% (\( p = 0.05 \)). Among non-migraineurs, the value of the formula \( (x/y) \times 100 \) for vertigo spells was lower than 50% in only 1 subject, in the range between 50-75% in 3 cases, while non-responders was 19. A chi square test on the number of responders to the therapy demonstrated significant difference between the 2 groups (\( p = 0.001 \)). A Mann-Whitney test demonstrated a significant decrease of vertigo spells in migraineurs than in non-migraineurs after combined therapy (\( p = 0.003 \)). Finally, in the sample of MD subjects with migraine, a correlation was seen between decrease of vertigo spells and headaches (\( p = 0.03 \)).

Discussion

As previously reported, migraine and MD often present with a comorbidity \(^{17}\). Moreover, around 51% of migraineurs suffer from vertigo or dizziness \(^{18,19}\). In some cases, differential diagnosis between MD and VM is complicated \(^{11}\), and relies mostly on audiometric exam \(^{20}\). However, a fluctuating low-frequency hearing loss has also been described in vestibular migraine \(^{10}\). Calcium-channel blockers have been demonstrated to be useful in migraine prophylaxis \(^{31}\), and there is evidence of efficacy of antimigrainous drugs (including Ca\(^{2+}\)-blockers) in preventing vertigo spells \(^{22}\). Above all, cinnarizine has been reported to ameliorate vestibular vertigo \(^{23}\), and both cochlear and vestibular symptoms have been reported to improve in MD sufferers \(^{21,24}\). Cinnarizine has long been believed to act through a direct block of voltage-gated Ca\(^{2+}\) currents \(^{25}\). A recent work, however, suggests that its main action is an inhibition of K\(^+\) currents, which may be activated in case of endolymphatic hydrops \(^{26}\). Flunarizine has also been shown to be effective in peripheral vertigo due to its calcium entry blocking properties provoking an increase in inner ear perfusion \(^{27}\). A recent retrospective study reported that MD patients undergoing prophylactic therapy with an association of nimodipine and betahistine presented a decreased number of vertigo spells compared to patients receiving betahistine alone \(^{16}\).

Our study confirms the efficacy of the association of betahistine and a Ca\(^{2+}\)-blocker in both MD patients with and without migraine, although significantly better results were obtained in migraineurs. Nonetheless, hearing loss progressed without beneficial effects in either group. Two possibilities should be considered to explain our findings. It has been suggested that the association of the two diseases could depend on a vascular alteration. Vasospasm has long been considered a characteristic of some migraine-associated features (such as visual auras) \(^{28}\). Some authors propose that migraine vasospasm causes ischaemic damage of small arteries of the inner ear, and endolymphatic hydrops develops on the previously damaged ear \(^{29}\). MD, therefore, would complicate migraine \(^{30}\). On the other hand, migraine may have an impact on frequency of MD attacks. MD patients refer increased spells in the catamenial period, similarly to when migraineurs experience headache more frequently \(^{31}\). The occasional low-frequency hearing loss in young women suffering from migraine has also been described mainly during the menstrual period \(^{11}\). In both pathogenic theories, Ca\(^{2+}\)-blockers should be useful in preventing MD spells. A common underlying susceptibility to the two diseases may be explained by the importance of calcium and other ions in both disorders. Ion channels in the inner ear are

### Table I

|                       | Betahistine       | Betahistine + cinnarizine | P value |
|-----------------------|-------------------|--------------------------|---------|
| Vertigo spells        | 9.4 ± 4.3         | 3.8 ± 3.4                | \( p = 0.0001 \) |
| Headaches             | 3 ± 1.9           | 1 ± 0.6                  | \( p = 0.0001 \) |
| PTA mean value        | 45.7 ± 8          | 53.4 ± 7.8               | \( p = 0.001 \) |

### Table II

|                       | Betahistine       | Betahistine + cinnarizine | P value |
|-----------------------|-------------------|--------------------------|---------|
| Vertigo spells        | 6.8 ± 3.5         | 5.9 ± 3.9                | \( p = 0.01 \) |
| PTA mean value        | 50.5 ± 7.5        | 55.8 ± 9.2               | \( p = 0.002 \) |
essential for the high potassium-concentration needed for endolymph maintenance. Both elevated and reduced concentrations of Ca\(^{2+}\) have been shown to suppress transduction currents.\(^ {12} \)\(^ {33} \) It has been reported that mice lacking Ca\(^{2+}\) channels suffer from delayed-onset hearing loss.\(^ {34} \) Moreover, experimentally induced endolymphatic hydrops in guinea pigs was accompanied by increased Ca\(^{2+}\) level in the vestibular end-organ.\(^ {35} \) This study, although performed on a small sample, underlines the different effects of cinnarizine in MD patients with and without migraine; it also infers a different action of cinnarizine on vestibular and cochlear symptoms in MD. Further studies are needed to define the origin of this disparity.

Conclusions

Our data confirm the efficacy of association of betahistine and cinnarizine in prophylaxis of MD, especially with concomitant vestibular migraine; further studies should confirm if prevention of migraine in these subjects may play a role in reduction of vertigo spells.

Acknowledgements

We thank professor Eugenio Mira, Department of Otolaryngology, University of Pavia, Italy, for his encouragement and suggestions.

References

1. Sajjadi H, Paparella MM. Ménière’s disease. Lancet 2008;372:406-14.
2. Merchant S, Adams J, Nadol J. Pathophysiology of Ménière’s syndrome: are symptoms caused by endolymphatic hydrops? Otol Neurotol 2005;26:74-81.
3. Committee on Hearing and Equilibrium. Guidelines for the diagnosis and evaluation of therapy in Ménière’s disease. Otolaryngol Head Neck Surg 1995;113:181-5.
4. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
5. Rassekh CH, Harker LA. The prevalence of migraine in Ménière’s disease. Laryngoscope 1992;102:135-8.
6. Radlke A, Lempert T, Gresty MA, et al. Migraine and Ménière’s disease. Neurology 2002;59:1700-4.
7. Ménière P. Pathologie auriculaire: memoires sur une lesion de l’oreille interne donnant lieu a des symptomes de congestion cerebrale apoplectiforme. Gaz Med Paris 1861;16:597-601.
8. Neff BA, Staab JP, Eggers SD, et al. Auditory and vestibular symptoms and chronic subjective dizziness in patients with Ménière’s disease, vestibular migraine, and Ménière’s disease with concomitant vestibular migraine. Otol Neurotol 2012;33:1235-44.
9. Lempert T, Olesen J, Furman J, et al. Vestibular migraine: diagnostic criteria. J Vestib Res 2012;22:167-72.
10. Battista RA. Audiometric findings of patients with migraine-associated dizziness. Otol Neurotol 2004;25:987-92.
11. Teggi R, Fabiano B, Recanati P, et al. Case report on two patients with episodic vertigo, fluctuating hearing loss and migraine responding to prophylactic drugs for migraine. Ménière’s disease or migraine associated vertigo? Acta Otorhinolaryngol Ital 2010;30:217.
12. Lezuis F, Adron C, Mansmann U, et al. High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Ménière’s disease: a case series. Eur Arch Otorhinolaryngol 2011;268:1237-40.
13. Della Pepa C, Guidetti G, Eandi M. Betahistine in the treatment of vertiginous syndromes: a meta-analysis. Acta Otorhinolaryngol Ital. 2006;26:208-15.
14. Silberstein SD, Holland S, Freitag F, et al. Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337-45.
15. Djelilovic-Vranić J, Alajbegović A, Tiric-Cambara M, et al. Betahistine or Cinnarizine for treatment of Ménière’s disease. Med Arch 2012;66:396-8.
16. Monzani D, Barillari MR, Alicandri Ciufelli M, et al. 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. Acta Otorhinolaryngol Ital 2012;32:393-43.
17. Ikekwe TS, Fasunla JA, Ikekwe PU, et al. Migraine and Ménière’s disease: two different phenomena with frequently observed concomitant occurrences. J Natl Med Assoc 2008;100:334-8.
18. Vuković V, Plavec D, Galinović I, et al. Prevalence of vertigo, dizziness, and migrainous vertigo in patients with migraine. Headache 2007;47:1427-35.
19. Parker W. Ménière’s disease. Etiologic considerations. Arch Otolaryngol Head Neck Surg 1995;121:377-82.
20. Boyev KP. Ménière’s disease or migraine? The clinical significance of fluctuating hearing loss with vertigo. Arch Otolaryngol Head Neck Surg 2005;131:457-9.
21. Snow V, Weiss K, Wall EM, et al. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med 2002;137:840-9.
22. Bikhazi P, Jackson C, Ruckenstein MJ. Efficacy of antimigrainous therapy in the treatment of migraine-associated dizziness. Am J Otol 1997;18:350-4.
23. Ganança MM, Caovilla HH, Munhoz MS, et al. Optimizing the pharmacological component of integrated balance therapy. Braz J Otorinolaryngol 2007;73:12-8.
24. Novotný M, Kostrica R. Fixed combination of cinnarizine and dimenhydrinate versus betahistine dimesylate in the treatment of Ménière’s disease: a randomized, double-blind, parallel group clinical study. Int Tinnitus J 2002;8:115-23.
25. Arab SF, Düwel P, Jüngling E, et al. Inhibition of voltage-gated calcium currents in type II vestibular hair cells by cinnarizine. Naunyn Schmiedebergs Arch Pharmacol 2004;369:570-5.
Haasler T, Homann G, Duong Dinh TA, et al. Pharmacological modulation of transmitter release by inhibition of pressure-dependent potassium currents in vestibular hair cells. Naunyn Schmiedebergs Arch Pharmacol 2009;380:531-8.

Olesen J. Calcium antagonists in migraine and vertigo. Possible mechanisms of action and review of clinical trials. Eur Neurol 1990;30(Suppl 2):31-4.

Viirre E, Baloh RW. Migraine as a cause of sudden hearing loss. Headache 1996;36:24-8.

Baloh RW. Neurotology of migraine. Headache 1997;37:615-21.

Cha YH, Kane MJ, Baloh RW. Familial clustering of migraine, episodic vertigo, and Ménière’s disease. Otol Neurotol 2008;29:93-6.

Andrews JC, Honrubia V. Premenstrual exacerbation of Ménière’s disease revisited. Otolaryngol Clin North Am 2010;43:1029-40.

Ohmori H. Mechano-electrical transduction currents in isolated vestibular hair cells of the chick. J Physiol 1985;359:189-217.

Tanaka Y, Asanuma A, Yanagisawa K. Potentials of outer hair cells and their membrane properties in cationic environments. Hear Res 1980;2:431-8.

Tabuchi K, Suzuki M, Mizuno A, et al. Hearing impairment in TRPV4 knockout mice. Neurosci Lett 2005;382:304-8.

Meyer zum Gottesberge-Orsulakova AM, Kaufmann R. Is an imbalanced calcium-homeostasis responsible for the experimentally induced endolymphatic hydrops? Acta Otolaryngol 1986;102:93-8.

Received: March 30, 2014 - Accepted: May 3, 2014