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

RIASSUNTO

La betaistina e i calcio-antagonisti si sono dimostrati efficaci nella profilassi della Sindrome di Ménière; i calcio-antagonisti sono utilizzati anche nella prevenzione degli episodi di cefalea emicranica. Scopo del nostro lavoro è stato quello di stabilire l'efficacia della terapia combinata con cinnarizina e betaistina nella prevenzione delle crisi vertiginose in un gruppo di pazienti affetti da Sindrome di Ménière senza e con comorbidità per emicrania. Cinquantadue pazienti affetti da Sindrome di Ménière, poco responsivi alla sola terapia con betaistina in un periodo di 6 mesi, sono stati inclusi nello studio, 29 dei quali emicranici. Nei 6 mesi successivi è stata effettuata terapia combinata con betaistina (48 mg al giorno) e cinnarizina 20 mg due volte al giorno per 1 mese, 20 mg al giorno per 2 settimane e 20 mg a giorni alterni per 2 ulteriori settimane; lo schema terapeutico è stato indi ripetuto. I dati relativi alla frequenza delle crisi vertiginose sono stati collezionati nei 6 mesi successivi. In entrambi i gruppi è stato dimostrato un decremento delle crisi vertiginose (da 9.4 a 3.8 in 6 mesi e da 6.8 a 5.9 in 6 mesi rispettivamente nel gruppo con e senza comorbidità per emicrania; le crisi di cefalea si sono inoltre ridotte da 3.8 a 1 in 6 mesi). È stata evidenziata una correlazione tra la diminuzione degli attacchi di vertigine ed emicrania. I nostri dati sottolineano un ruolo terapeutico della cinnarizina nella prevenzione degli attacchi di vertigine soprattutto nei soggetti con comorbidità emicranica.

PAROLE CHIAVE: *Sindrome di Ménière • Emicrania • Terapia • Calcio-antagonisti • Cinnarizina • Betaistina*

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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 mechanism [1], although according to some authors hydrops may be the consequence of a primitive damage of the inner ear [2].

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 vertigo [3]. 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 phono- and photophobia, with a prevalence of 15-17% in women and 5-8% in men [4].

Epidemiological studies have shown an association between MD and migraine, variously reported between 43% and 56% [5 6] and described by Prosper Ménière himself [7]. The high frequency of migraine in MD population may underline a pathophysiological link between the two disorders [8]. Recent papers have focused on increasing evidence that migraine per se may provoke episodic vertigo, and clinical entity is defined as vestibular migraine (VM) [9].

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 [10]. In some cases, at the initial stages of episodic vertigo, differential diagnosis between MD and VM may be a puzzling dilemma [11].

Betahistine has been demonstrated to be useful in prevention of episodic vertigo in MD [12 13], while calcium-blockers are among the most widely used drugs in prophylactic therapy of migraine [14]. 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 [15]. A recent report focused on the possibility that nimodipine may increase efficacy of betahistine in prevention of vertigo spells in MD patients [16].

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 monotherapy 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, thyroids, 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

Table I. Number of vertigo spells, headaches and PTA average (db HL) in 6 months of monotherapy and 6 months of combined therapy in the sample of MD patients with migraine (n = 29).

	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. Number of vertigo spells, headaches and PTA average (db HL) in 6 months of monotherapy and 6 months of combined therapy in the sample of MD patients without migraine (n = 23).

	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

summarised 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) x 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) x 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) x 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 [21], 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 [23 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 receving 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 [31]. 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

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 [32 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 comorbidity with migraine; further studies should confirm if prevention of migraine in these subjects may play a role in reduction of vertigo spells.

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