

TREATMENT OF TINNITUS AND DIZZINESS ASSOCIATED VERTEBROBASILAR INSUFFICIENCY WITH A FIXED COMBINATION OF CINNARIZINE AND DIMENHYDRINATE

FRANCESCO MARTINES¹, MONICA AGRIFOGLIO², DANIELA BENTIVEGNA¹, MARIANNA MUCIA², PIETRO SALVAGO¹, FEDERICO SIRECI¹, ANTONELLA BALLACCHINO²

¹University of Palermo, BioNeC Department, Section of Otolaryngology, ²University of Palermo, Di.Bi.Me.F. Department, Audiology Section, Palermo, Italy

[Trattamento del tinnitus e della vertigine associata a insufficienza vertebrobasilare con una combinazione standard di cinnarizina e dimenidrate]

ABSTRACT

Seventy-eight consecutive subjects, 43 males and 35 females, ranging from 43 to 87 years of age suffering from dizziness and/or tinnitus due to vertebrobasilar insufficiency without other central nervous system diseases were treated with fixed combination of cinnarizine and dimenhydrinate two times a day and for two months.

Data were collected considering the following parameters: age, sex, vestibular symptoms (unsteadiness, staggering, tendency to fall, swaying, vertigo due to change of position, bowing, walking, eye movements), headache, tinnitus, impaired hearing and aural fullness. Patients evaluated their vertigo symptoms and/or tinnitus intensities using a graded 3- point visual analog scale ranging from 1 (no symptoms) to 3 (strong symptoms) and their impact of life with classical tinnitus handicap inventory (THI) and dizziness handicap inventory (DHI) at first appointment, during the treatment and after therapy. The results of THI and DHI evidenced a statistical significant improvement either for tinnitus ($t = 3.57$; $p < 0.001$) and for vestibular symptoms ($t = 4.12$; $p < 0.001$); in particular at the final examination, of the 62 patients suffered from tinnitus, the 38.71% (24 cases) did not present the disorder while of the vestibular symptoms; unsteadiness and staggering both evidenced in 65/78 subjects (83.33%) at the beginning of the therapy, disappeared in the 43.08%.

In conclusion dual action of the treatment showed improvement of tinnitus and dizziness symptoms, which was confirmed either by symptoms' reduction and by THI and DHI score.

Key words: Tinnitus, dizziness, vertebrobasilar insufficiency, cinnarizine, dimenhydrinate.

Received September 11, 2012; Accepted September 17, 2012

Introduction

Epidemiological studies showed that about one third of the population, particularly the elderly, experiences dizziness and tinnitus at least once in their life and about 1-5% develop serious psychosocial complications^(1,2).

While tinnitus is defined as an auditory phantom sensations, a "perception of a sound which result exclusively from activity within the nervous system without any corresponding mechanical, vibratory activity within the cochlea"⁽³⁾, and usually represents an hearing deficit related phenomena, dizziness is a pathological dysfunction of the balance maintenance that is related to unsteadiness, staggering, tendency to fall, etc^(3,4).

As stated above, when persistent these disorders may rapidly become a source of serious disturbances and handicap at psychological and socio-professional levels; in fact in 1-3% of the general population, the tinnitus and dizziness affect the quality of life, involving sleep disturbance, work impairment and psychiatric distress⁽⁵⁾.

In half of cases this association may find a possible etiology in the vertebrobasilar insufficiency that could affect either in acute and chronic presentation; in the first one it could be accompanied with sudden hearing loss while in the second ones the 50% of cases suffer from hearing loss^(6,7).

Both acute and chronic clinical manifestations are lead to failure of microcirculation; in fact the so known "vertebrobasilar system" is responsible for

the blood supply of 10 cranial nerves, all ascending and descending tracts, parts of the cortical hemispheres, the cerebellum, the brainstem reticular formation, and the end-organs of hearing and balance (cochlea, semicircular canals, otolith system and vestibular sensory cells)^(8,9). Therefore an insufficient blood supply, causes alteration and/or death of these structures like hair cells causing a discontinuous aberrant neuronal activity characterized by unsteadiness and tinnitus due to peripheral and/or central dysfunction. For this reason it would be useful to act at both central and peripheral, especially in elderly where the atherosclerosis of the supra-aortic trunks with insufficient collateral circulation and compression of vertebral arteries by cervical spondylosis with the subclavian steal syndrome are common clinical reports^(3,10).

The aim of this study was to focus the audiovestibular disorders, on patients suffering from tinnitus and dizziness, in absence of organic central or systemic diseases in time, treating them with fixed combination - CINNARIZINE AND DIMENHYDRINATE two times a day for 60 consecutive days.

Materials and methods

The study was conducted by Department of Audiology of Palermo University on 78 consecutive subjects, 43 males and 35 females, ranging from 43 to 87 years of age suffering from dizziness and/or tinnitus with exclusion of central nervous system diseases.

As for the analysis of data collected, the following parameters were considered: age, sex, vestibular symptoms (unsteadiness, staggering, tendency to fall, swaying, vertigo due to change of position, bowing, walking, eye movements), headache, tinnitus, impaired hearing, aural fullness. Patients evaluated their vertigo symptoms and/or tinnitus intensities using a graded 3- point visual analog scale ranging from 1 (no symptoms) to 3 (strong symptoms).

The audio/vestibular system was studied through liminar audiometry (considering the frequencies 0.5-1-2-4 kHz) and clinical vestibular examination tests (bed side examination).

To value the perceived severity of dizziness and tinnitus and its impact of life and the therapy efficacy, the subjects were invited to compile Dizziness Handicap Inventory (DHI) and Tinnitus Handicap Inventory (THI). These tool are a 25-item

survey that are composed of three subscales: a functional subscale (12 items), an emotional subscale (8 items) and a somatic response subscale (5 items) which address role and physical functioning, psychological distress, desperation and loss of control, respectively. 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/dizziness handicap and 100 the worst patients' annoyance.

Overall patients were subjected to an entry examination (first appointment, before start of treatment), an intermediate examination (second visit, after fifteen + 3 days), and a final examination at the end of treatment (60 + 5 days). On the occasion of each visit, patients underwent an efficacy evaluation that was based primarily on the patient's assessments of the intensities of their audiovestibular symptoms. In addition, it was investigated the audiometric threshold and the bed side examination.

For the statistical analysis "Student's t-test", linear regression (r value) and/or ANOVA test were used, following usual conditions of application. Significance was set at 0.05.

Results

Of the 78 patients, 43 (55.19%) males and 35 (44.87%) females, aged between 43 and 87 with a mean age of 65.30. In 85.9% (67 cases) the subjects underwent ENT examination for vestibular disorders; of them in 76.12% corresponding to 51 cases this disorder was associated to tinnitus while in 16 patients the annoyance was isolated. In the other 11 cases (14.1%) the only disorder resulted the tinnitus. Table 1 shows the distribution of the vestibular symptoms reported by cohort; in particular at the moment of the first examination, unsteadiness, staggering and bowing evidenced the higher percentage values of strong intensity (respectively of 50%, 50%, 51.28%).

The study of the mean and median vertigo scores (figure 1) also confirm as stated above while the tendency to fall, vertigo due to change position, head movements, walking and swaying presented lower scores. Through the DHI questionnaire the patients, were divided into five severity levels.

With a percentage of 52.56% (41 cases) catastrophic level was the main represented, followed by the severe level with 16.66% corresponding to 13 subjects.

Audiovestibular symptoms	Subjective scale range	Examination (days)			Statistical analysis (r)
		T 0	T 15 + 3	T 60 + 5	
UNSTEADINESS	1	16.66%	37.18%	52.56%	0.99
	2	33.33%	34.62%	39.74%	
	3	50%	28.20%	7.69%	
STAGGERING	1	16.66%	37.18%	52.56%	0.99
	2	33.33%	34.62%	39.74%	
	3	50%	28.20%	7.69%	
TENDENCY TO FALL	1	52.57%	66.66%	79.48%	0.98
	2	15.38%	19.23%	14.11%	
	3	32.05%	14.11%	6.41%	
SWAYING	1	37.18%	58.97%	73.08%	0.95
	2	34.62%	30.77%	19.23%	
	3	28.20%	10.26%	7.69%	
VERTIGO DUE TO CHANGE OF POSITION	1	50%	70.51%	80.77%	0.95
	2	14.11%	16.66%	16.66%	
	3	35.89%	12.82%	2.56%	
BOWING	1	33.33%	53.84%	74.36%	0.99
	2	15.38%	17.95%	19.23%	
	3	51.28%	29.49%	6.41%	
VERTIGO DUE TO WALKING	1	41.03%	58.97%	76.92%	0.99
	2	26.92%	20.51%	11.54%	
	3	32.05%	20.51%	11.54%	
VERTIGO DUE TO HEAD MOVEMENTS	1	42.31%	69.23%	75.64%	0.95
	2	20.51%	10.26%	17.95%	
	3	37.18%	20.51%	6.41%	
TINNITUS	1	20.51%	41.03%	51.28%	0.99
	2	33.33%	21.79%	37.18%	
	3	46.15%	41.03%	11.54%	
FULLNESS	1	53.84%	80.77%	94.87%	0.96
	2	21.79%	11.54%	5.13%	
	3	24.35%	7.6%	-	

Table 1: distribution of the audiovestibular symptoms during time and, correlation index (r) of the mean values.

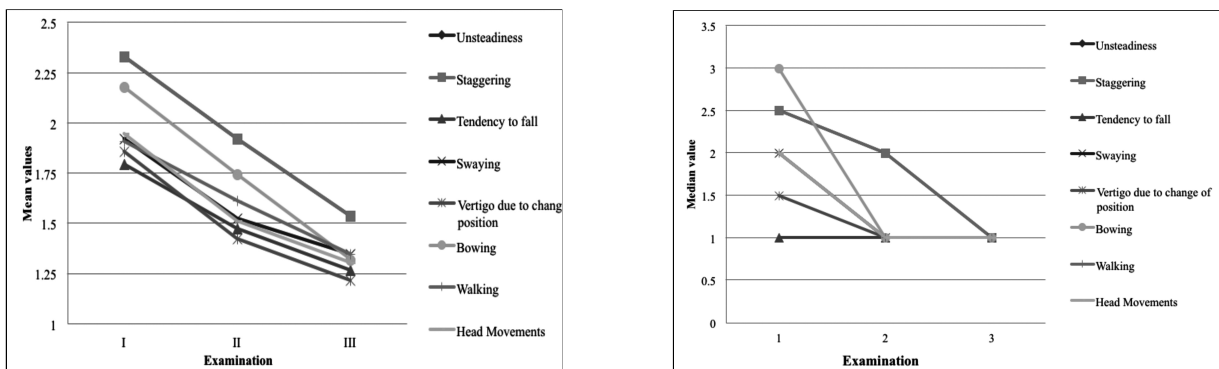


Fig. 1a- 1b: Study and progression of the mean (a) and median (b) vertigo scores.

The 79.48% of cases corresponding to 62/78 suffered from tinnitus at first examination; of them 36 (58.06%) had a level 3 of tinnitus. The tinnitus symptom accompanied hearing loss in the 90.32%

of cases (56 patients). The audiological assessment evidenced a slight hearing loss for the frequencies 0,5, 1 and 2 KHz while a middle hearing loss for 4 kHz. With a percentage of 29,49% (23 cases) cata-

strophic level was the main represented at THI results, followed by the severe level with 28,20% corresponding to 22 subjects.

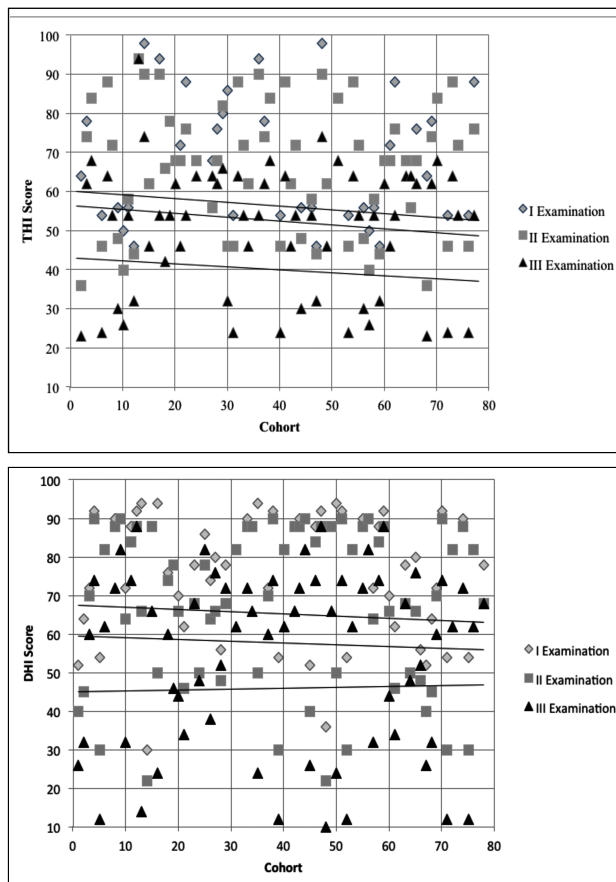


Fig. 2a- 2b: a) THI score – Cohort distribution; b) DHI score - Cohort distribution.

Overall patients were treated with fixed combination - CINNARIZINE AND DIMENHYDRINATE two times a day for two months and, were examined two times: during the treatment (15 days + 3) and at the end of the protocol therapy.

From the data it was evidenced a statistical significant improvement either of the tinnitus and of the vestibular symptoms. In fact at the final examination, of the patients suffered from tinnitus, the 38.71% (24/62 cases) did not present the disorder, while the 14.51% (9/62) did not observed any improvement ($t = 3.72$; $p < 0.001$). These data are confirmed by THI results; with mean values of 56.41, 52.49 and 40.05 respectively at first examination, during the treatment and at the end of the therapy, only the 1.28% of the subjects presented a 5 grade of disability after treatment while in 26.51% the disorder disappeared ($t = 3.57$; $p < 0.001$) (figure 2a).

Of the vestibular symptoms, unsteadiness and staggering both evidenced in 65/78 subjects

(83.33%) at the beginning of the therapy, disappeared in the 43.08% corresponding to 28 cases, improved in 47.69% while remained unchanged in 9.23%. Bowing symptom presented in 52/78 cases (66.66%) disappeared in 61.53%, improved in 28.54% and unchanged in 9.61%. DHI score mean values resulted respectively of 65.25, 57.77 and 45.87 at first appointment, at intermediate examination and at the end of treatment ($t = 4.12$; $p < 0.001$) (figure 2b).

Finally even if it was observed a slight improvement of the hearing threshold level between the first and the final examination, especially for the 4 KHz (first examination - 54 dB HL; after treatment - 49.49 dB HL), the statistical study of the means did not result significant ($p > 0.01$).

Discussion

Tinnitus and dizziness are a multifactorial symptoms provoking an important decrease in the quality of life^(11,12); the etiology is not yet fully understood because there are different local and/or systemic triggers (cardiovascular, vertebrobasilar insufficiency, metabolic, etc.)^(13,14). The epidemiological data have generally supported a strong association between tinnitus and dizziness especially in the higher ages, probably due to an higher prevalence of associated disorders that act as predisposing conditions^(15,16,17).

When present, the sensorineural hearing loss is usually limited to the high frequencies (89.74% of cases in our study), probably lead to tonotopic map of acoustic nerve that plays a significant role in the pitch of tinnitus. The fact that the pitch of tinnitus corresponds to the injured area of the nerve in its tonotopic map was also referred by Savastano, Satar et al.^(18,19,20).

According to literature, vestibular symptoms in patients with impaired vascular are mainly characterized by a sense of instability, 83.4% (65/79 patients) of cases, rather than paroxysmal vertigo, which makes them insecure.

In this study in fact, were included patients suffering from vascular both peripheral and central referring a clear impairment of daily activities and a higher psychological distress that has been shown by scores of DHI and THI.

Because the cohort would be mainly affected by alterations in the microcirculation with impairment in both central and peripheral region, the two active components of the fixed combination have

distinct pharmacological properties that complement one another synergistically; while cinnarizine acts predominantly on the peripheral vestibular labyrinth by affecting local calcium ion flux, dimenhydrinate is primarily effective on central structures, mainly the vestibular nuclei and adjacent vegetative centres in the brainstem⁽²¹⁾.

As demonstrated by Otto et al. the calcium antagonist cinnarizine, acts by enhancing circulation in the peripheral vestibular organ and in compromised intra and extracranial areas; the action of cinnarizine is reinforced by dimenhydrinate because inhibits the spreading of impulses at the medullar vestibular nuclei^(22,23,24). In particular, in Otto's study were evaluated three groups of patients for a total of 37, of which 11 were treated with the fixed combination, 13 with betahistine and 13 with placebo. The results⁽²⁵⁾ showed a statistically significant improvement in the first group of patients just after one week of treatment respect to those treated with betahistine and placebo⁽⁸⁾.

Also in our cohort it was evidenced, as reported by patients' responses at DHI and THI, a slight improvement of dizziness and tinnitus after two weeks of treatment but it resulted significant only after two months of treatment. The physiopathological correlate of these results, in patients suffering from tinnitus and dizziness in presence of microcirculation disorders, can be found in the particular blood supply end of the cochlea.

Therefore the prompt therapy targeted at anterior labyrinth artery reperfusion should prevent hair cells' death and the 'onset of acute tinnitus, while a long term therapy leads to recovered labyrinthine function and it's maintenance.

Conclusions

The present results, according to literature data, have proven that the fixed combination of cinnarizine and dimenhydrinate is an effective therapeutic option in treating vertigo and tinnitus due to vertebrobasilar insufficiency.

Dual action of the treatment showed improvement of tinnitus and dizziness symptoms, which was confirmed either by symptoms' reduction (38.71% and 43.08% respectively for tinnitus and dizziness suffered were cured) and by the THI and DHI score at final examination ($p < 0.001$).

References

- 1) Martines F, Bentivegna D, Di Piazza F, et al. *Investigation of tinnitus patients in Italy: clinical and audiological characteristics*. Int J Otolaryngol 2010; 2010: 265861.
- 2) Salvago P, Ballacchino A, Agrifoglio M, et al. *Tinnitus patients: etiologic, audiological and psychological profile*. Acta Medica Mediterranea 2012; 28: 171-175.
- 3) Jastreboff PJ, *Phantom auditory perception (tinnitus): mechanisms of generation and perception*. Neurosci Res 1990; 8: 221-254.
- 4) Martines F, Maira E, Ferrara S. *Age-related hearing impairment (ARHI): a common sensory deficit in the elderly*. Acta Medica Mediterranea 2011, 27: 47.
- 5) Martines F, Bentivegna D, Martines E et al. *Characteristics of tinnitus with or without hearing loss: clinical observation in Sicilian tinnitus patients*. Auris Nasus Larynx 2010; 37: 685-693.
- 6) Martines F, Dispenza F, Gagliardo C, et al. *Sudden sensorineural hearing loss as prodromal symptom of anterior inferior cerebellar artery infarction*. ORL J Otorhinolaryngol Relat Spec 2011; 73: 137-140.
- 7) Martines F, Bentivegna D, Martines E, et al. *Assessing audiological, pathophysiological variables in tinnitus patients with or without hearing loss*. Eur Arch Otorhinolaryngol 2010; 267: 1685-1693.
- 8) Otto V, Fischer B, Schwarz M, et al. *Treatment of vertebrobasilar insufficiency-associated vertigo with a fixed combination of cinnarizine and dimenhydrinate*. International tinnitus Journal 2008;14: 57-67.
- 9) Baloh RW, *The dizzy patient*. Postgrad Med 1999; 105:161-172.
- 10) Eggermont JJ, *Central tinnitus*. Auris Nasus Larynx 2003; 30 Suppl: 7-S12.
- 11) Maggio M, Martines F, Mucia M, et al. *A Multifactorial pattern for the understanding of the psychological development of the child with impaired hearing and its clinical-therapeutic implications*. Acta Pediatrica Mediterranea 2006; 22: 41-44.
- 12) Cespuglio D, Maggio M, Maggio O, et al. *Tinnitus: epidemiology*, Acta Medica Mediterranea 2005; 21: 49-51.
- 13) Martines F, Martinciglio G, Bucalo C et al. *Neurovascular conflict in patient with tinnitus and essential hypertension: case report*. Otorinolaringol 2008; 58: 191-196.
- 14) Martines F, Pangaro A, Martines E, *Ménière's diseases and neurovascular cross-compression: case report*. Otorinolaringol 2009; 59: 65-69.
- 15) Axelsson A, and Ringdahl A, *Tinnitus: a study of its prevalence and characteristics*, British Journal of Audiology 1989; 23: 53-62.
- 16) Davis A, and El Rafeie A, *Epidemiology of tinnitus*, Tinnitus Handbook, pp. 1-23, Singular Publishing Group, San Diego, Calif., USA, 2000.
- 17) Pilgramm M, Rychlick R, Lebesch H, et al, *Tinnitus in the federal Republic of Germany: a representative epidemiological study*, in Proceeding of the 6th International Tinnitus Seminar, pp. 64-67, Cambridge, UK, 1999.
- 18) Savastano M, *Tinnitus with or without hearing loss: are its characteristics different?* European Archives of Otorhinolaryngology 2008; 265: 1295-1300.

- 19) Satar B, Kapkin O, and Ozkaptan Y. *Evaluation of cochlear function in patients with normal hearing and tinnitus: a distortion product otoacoustic emission study*, Kulak Burun Bogaz Ihtisas Dergisi 2003; 10: 177-182.
- 20) Henry JA, Schechter MA, Regelein RT et al, *Veterans and tinnitus*, in *Tinnitus: Theory and Management*, J.B. Snow Jr, Ed., pp. 337-355, McGraw Hill, New York, NY, USA, 2004.
- 21) Pytel J, Nagy G, Tóth A, et al. *Efficacy and Tolerability of a Fixed Low-Dose Combination of Cinnarizine and Dimenhydrinate in the Treatment of Vertigo: A 4-Week, Randomized, Double-Blind, Active-and Placebo-Controlled, Parallel-Group, Outpatient Study*, Clin Ther 2007; 29:84-98.
- 22) Godfraind T, Towse G, and van Nueten JM, *Cinnarizine: A selective calcium entry blocker*. Drugs Today 1982; 18: 27-42.
- 23) Oosterveld WJ. *Cinnarizine in the vertiginous Syndrome*. International Congress and Symposium Series N°33. London: Royal Society of Medicine and Academic Press Inc 1979: 29-37.
- 24) Jaiu BP and Wang SC, *Effect of diphenhydramine and dimenhydrinate on vestibular neuronal activity of cat: a search for the locus of their antimotion sickness action*. J Pharmacol Exp Ther 1971; 176: 718-724.
- 25) Sireci F, Ballacchino A, Agrifoglio M, et al. *Psychopathologic diseases in patients with tinnitus: a case-control of an outpatient cohort*. Acta Medica Mediterranea 2012; 28: 167-170.

Request reprints from:
Dr. FRANCESCO MARTINES
Via Autonomia Siciliana, 70
90143 Palermo
(Italy)