International Tinnitus Journal, Vol. 8, No. 1, 50–53 (2002)

Clonazepam in the Pharmacological Treatment of Vertigo and Tinnitus

Mauricio Malavasi Ganança, Heloisa Helena Caovilla, Fernando Freitas Ganança, Cristina Freitas Ganança, Mário Sérgio Lei Munhoz, Maria Leonor Garcia da Silva, and Flávio Serafini

Division of Neurootology, Department of Otorhinolaryngology and Communicative Disorders, Universidade Federal de São Paulo—Escola Paulista de Medicina, São Paulo, Brazil

Abstract: We carried out a retrospective survey of 25 years of clinical experience with the use of clonazepam as a vestibular and tinnitus suppressant in the pharmacological treatment of vestibular or cochleovestibular disorders due to different causes. We reviewed the medical records of 3,357 outpatients treated with a 0.5- or 1.0-mg daily dosage of oral clonazepam during 60–180 days. Complete or substantial control of vertigo or nonvertiginous dizziness was achieved in 77.4% of the vertigo patients. Tinnitus was improved in 32.0% of the tinnitus patients. Light or mild drowsiness, depression, nightmares, or lowering of libido, reported by 16.9% of the patients as adverse side effects, tended to subside with continued therapy. We concluded that clonazepam is a very useful and safe drug for the symptomatic treatment of patients suffering from cochleovestibular disorders.

Key Words: clonazepam; tinnitus; treatment; vertigo

The pharmacological profile of clonazepam is similar to that of other benzodiazepines. It has anxiolytic, sedative, and serotoninergic properties. Clonazepam stimulates central serotonin synthesis and facilitates γ-aminobutyric acid (GABA) transmission.

The usefulness of clonazepam seems to be related to its high binding affinity and its long-acting effects. These clonazepam abilities may play a role in its efficacy in a variety of clinical conditions other than seizures. Clinical experience has shown that clonazepam may be beneficial in the treatment of patients suffering from benzodiazepine dependence, mania, panic disorder with or without agoraphobia, nystagmus-induced oscillopsia, organic brain syndromes, chronic pain, and hyperexplexia [1].

Since 1976, clonazepam has been shown to be an excellent, safe, and extremely efficient vestibular suppressant, even when administered in small dosages. The usefulness of clonazepam in the treatment of vertigo was mentioned by several authors [2–10]. Clonazepam can also be useful in the management of tinnitus, hyperacusis, phonophobia, or aural fullness [11–18].

A clear reduction in or cessation of nystagmus-induced oscillopsia due to downbeat or other primary-position nystagmus can be achieved with either single-dose or long-term clonazepam therapy. These effects seem to be mediated by direct action on the slow-phase velocity of the nystagmus [19]. Long-term therapy by clonazepam with a dosage of 1.0 mg twice daily can produce elimination of oscillopsia, relief of diplopia, and improvement of visual acuity in patients with downbeat nystagmus [20].

BACKGROUND

In the last 25 years, the favorable effects of clonazepam on vertigo and related symptoms have been evaluated in patients suffering from cochleovestibular disorders [21–27]. An inverse significant correlation between the therapeutic activity of clonazepam and its daily dosages

Reprint requests: Mauricio Malavasi Ganança, M.D., Ph.D., Rua Dr. Eduardo de Souza Aranha 99 cj 62. 04543-120, São Paulo, Brazil. Phone: 55 11 3044-1620; Fax: 55 11 3842-5523; E-mail: mauricio.gananca@globo.com

was verified; better clinical results were obtained with smaller doses (0.5 or 1.0 mg/day).

A placebo-controlled, double-blind, randomized trial was undertaken to assess the efficacy and safety of clonazepam in the treatment of vertigo of vestibular origin [28]. The trial was carried out in 63 outpatients. Clonazepam was prescribed to 34 patients, and the placebo was given to 29 patients. Clonazepam was given by oral route in doses of 0.5 mg three times daily over 30 days, 0.5 mg twice daily for 30 days more, and 0.5 mg daily in the last 30 days of the treatment.

The evaluation criteria were based on the subjective evolution of vertigo or dizziness (or both). At the end of therapy, the patients were classified as asymptomatic (complete remission), improved (partial remission), or unimproved (no change). The results were statistically assessed using the Chi-square test. Complete resolution or improvement of the vestibular symptoms was achieved in 85.3% of the patients (29 of 34) treated with clonazepam, whereas complete or partial remission of vertigo or dizziness (or both) was found in 58.6% of the patients (17 of 29) taking a placebo.

Mild or moderate drowsiness, especially at the beginning of the therapy, was reported by 50.0% of the patients treated with clonazepam (17 of 34) and by 17.2% of the patients taking placebo (5 of 29). Statistical analysis showed that clonazepam was significantly more active than the placebo in effecting the complete or partial remission of vertigo or dizziness. The authors concluded that clonazepam is an effective and well-tolerated drug for the symptomatic treatment of peripheral vestibular disorders.

A comparative study to assess the efficacy and safety of clonazepam, 0.5 mg three times daily, and cinnarizine, 25.0 mg three times daily, by the oral route over 60, 90, 120, or 180 days, was performed on 2,196 patients experiencing dizziness [29]. This trial has shown that 97.8% of the patients treated with clonazepam (1,972 of 2,016) and 88.9% of the patients treated with cinnarizine (160 of 180) either were considered to have improved at different degrees or were asymptomatic. Both drugs were found to exert a marked improvement in patients with dizziness. No significant difference could be established between the two drugs in comparing their results with 120 or 180 days of medication. However, a significant difference in favor of 60 or 90 days of clonazepam therapy was found. Side effects from the use of clonazepam were considered to be mild and well tolerated and less common and less intense than those derived from the use of cinnarizine; in no case did such effects necessitate the interruption of the medication.

A placebo-controlled investigation of the antivertiginous effect of the anticonvulsants clonazepam (0.5 mg/day), carbamazepine (100.0 mg/day), and phenytoin (30.0 mg/day) was carried out [30]. A total of 1,124 patients entered the study, 430 in the clonazepam group, 323 in the carbamazepine group, 309 in the phenytoin group, and 62 in the placebo group. The drugs were given at bedtime over 90 days in an outpatient-based evaluation. In that study, the antivertiginous effect of phenytoin (64.4% of improved patients [199 of 309]) could not be distinguished from that of placebo. It was verified that 40.3% of the patients who received placebo (25 of 62) have improved. Clonazepam (81.4% of improved patients [350 of 430]) and carbamazepine (71.2% of improved patients [230 of 323]) presented outcomes significantly better than those resulting from the placebo.

Patients with symptoms compatible with migraine-related vertigo or dizziness and anxiety disorders or panic attacks are appropriate candidates for clonazepam [31].

It is very likely that the benzodiazepine diazepam produces its favorable effects on vertigo by decreasing activity in the vestibular nuclei. Clonazepam enjoys an enhanced effect at this site, with less risk of dependency from long-term usage as compared to diazepam [32].

PATIENTS AND METHOD

We reviewed the medical records of 3,357 patients who suffered from vestibular disorders and had been treated with clonazepam as the only antivertigo medication. There were 2,080 female and 1,277 male patients aged 13–87 years (mean, 49 years). The average duration of neuro-otological symptoms was 1.6 years. Clonazepam was prescribed in a 0.5- or 1.0-mg daily oral dosage over 60–180 consecutive days in an outpatient-based evaluation.

Vertigo or dizziness, hearing loss, tinnitus, and other related symptoms were investigated in the patients' medical history. All patients received a thorough clinical evaluation, including disease history; ear, nose, and throat examination; tests of auditory function; and electronystagmography, before and after the treatment. The medical management also included etiological treatment when the cause was identified. The main evaluation criterion was patients' opinion of the treatment results. For the purposes of this study, the patients were classified as asymptomatic (complete remission of symptoms), improved (partial remission of symptoms), and unimproved (no change).

RESULTS

All 3,357 patients presented with vertigo or nonvertiginous dizziness (or both). We observed that complete or substantial control of vertigo or nonvertiginous dizziness was achieved in 2,598 (77.4%) of the patients treated

with clonazepam. Tinnitus was reported by 1,020 patients. The reduction or elimination of this symptom was reported by 326 (32.0%) of the treated patients.

Worsened symptoms after treatment were not observed. One or more adverse side effects were reported by 568 (16.9%) of the patients treated with clonazepam. Light or mild drowsiness was the main adverse event with the use of clonazepam; light depression, nightmares, and lowering of libido were other side effects observed. All adverse effects occurred at the onset phase of the treatment and were either substantially reduced or disappeared in a spontaneous way.

DISCUSSION

Clonazepam is a benzodiazepine that may have the potential to ameliorate or eliminate vertigo or dizziness. Several reports have described the successful use of clonazepam in the treatment of peripheral and central vestibular disorders. In comparison to placebo, clonazepam has demonstrated a significant effect in reducing vertigo. In an additional trial, the vestibular effects of clonazepam have been compared to those of cinnarizine. Comparing the outcomes of clonazepam and cinnarizine, both drugs were considered very useful in the medical treatment of vestibular disorders. Besides clonazepam's better outcomes in 60- or 90-day therapy, the adverse effects from the use of clonazepam were considered to be less frequent and less intense than those caused by the use of cinnarizine.

Despite of the antivertiginous activity demonstrated in clinical studies and in the neurootological routine, the beneficial vestibular suppressant effect of clonazepam is not quoted among its properties in reference textbooks of pharmacology. The results of the present retrospective study indicated that clonazepam was very helpful in improving vertigo or dizziness in most of the treated patients. Many patients also reported that their tinnitus was eliminated or that it was less troublesome with the use of clonazepam. Clonazepam caused only minor adverse events, which tended to subside gradually on continuation of therapy.

The outcomes of clinical experience led us to believe that drug therapy plays a significant role in the management of chronic vertigo and related symptoms. In cases in which there is a need for symptomatic therapy, the benzodiazepine clonazepam should be considered as a useful agent for optimal control of vestibular symptoms.

CONCLUSION

Clonazepam has been shown to be effective and safe in the medical management of neurootological disorders.

REFERENCES

1. Rosenbaum JF (ed). *Clonazepam Update: A Review of the Literature*, ed 2. Princeton: Excerpta Medica, 1996.
2. Mangabeira Albernaz PL, Ganança MM. Síndromes Vestibulares. In: *Guia Prático de Labirintologia*. São Paulo: Editamed, 1976.
3. Rascol O, Hain TC, Brefel C, et al. Antivertigo medications and drug-induced vertigo: A pharmacological review. *Drugs* 50(5):777–791, 1995.
4. Shepard NT, Telian AS. *Practical Management of the Balance Disorder Patient*. San Diego: Singular, 1996.
5. Baloh RW. *Dizziness, Hearing Loss, and Tinnitus*. Philadelphia: Davis, 1998.
6. Bhansali SA. Therapy: Medical Alternatives. In JA Goebel (ed), *Practical Management of the Dizzy Patient*. Philadelphia: Lippincott Williams & Wilkins, 2001:299–315.
7. Haybach PJ. *Ménière's Disease: What You Need to Know*. Portland: Vestibular Disorders Association, 1998:169.
8. Haybach PJ. *BPPV (Benign Paroxysmal Positional Vertigo): What You Need to Know*. Portland: Vestibular Disorders Association, 2000:180.
9. Moller MB. Selection criteria and treatment of patients with disabling positional vertigo. *Stereotact Funct Neurosurg* 68:270–273, 1997.
10. Ganança MM, Caovilla HH. Modern Trends in the Drug Treatment of Vertigo. In CF Claussen, T Haid, B Hofferberth (eds), *Equilibrium in Research, Clinical Equilibriometry and Modern Treatment*. Amsterdam: Elsevier Science, 2000:507–509.
11. Lechtenberg R, Shulman A. Benzodiazepines in the treatment of tinnitus. *J Laryngol* Suppl 9:272–277, 1984.
12. Ganança MM, Caovilla HH. The value of clonazepam in the treatment of tinnitus [abstract]. In *Abstracts of the First International Meeting for the Mediterranean Countries: Clinical Audiology '87*. Rosa Marini, Brindisi: Community of the Mediterranean Universities, 1987:143.
13. Szczepaniak WS, Moller AR. Effects of baclofen, clonazepam, and diazepam on tone exposure-induced hyperexcitability of the inferior colliculus in the rat: Possible therapeutic implications for pharmacological management of tinnitus and hyperacusis. *Hear Res* 97(1–2):46–53, 1996.
14. Coles R. Therapeutic Blind Alleys. In AJ Vernon (ed), *Tinnitus: Treatment and Relief*. Boston: Allyn & Bacon, 1997:8–19.
15. Boleloucky Z. Psychiatrie a Tinnitus. In A Hahn (ed), *Proceedings of the Tinnitus 2000 Mezinárodni Sympozium*. Prague: Vesmír, 2000:14–17.
16. Solomon D. Distinguishing and treating causes of central vertigo. *Otolaryngol Clin North Am* 33(3):579–601, 2000.
17. Shulman A, Strashun AM, Seibyl JP. $GABA_A$ benzodiazepine deficiency syndrome in tinnitus patients. Presented at the Seventeenth International Meeting of the Neurootological and Equilibriometric Society, Bad Kissingen, Germany, March 24–26, 2000.
18. Ganança MM, Ganança FF. Substâncias Antivertigino-

sas. In MM Ganança, HH Caovilla, MSL Munhoz, MLG Silva (eds), *Estratégias Terapêuticas em Otoneurologia*. São Paulo: Atheneu, 2000.

19. Currie JN, Matsuo V. The use of clonazepam in the treatment of nystagmus-induced oscillopsia. *Ophthalmology* 93:924, 1986.
20. Young Y-H, Huang T-W. Role of clonazepam in the treatment of idiopathic downbeat nystagmus. *Laryngoscope* 111:1490–1493, 2001.
21. Ganança MM, Caovilla HH. Clonazepam in the treatment of cochlear and vestibular syndromes [abstract]. In *Proceedings of the Eighteenth International Congress of Audiology*. Prague: International Society of Audiology, Czechoslovak Otolaryngological Society, 1986:77.
22. Ganança MM, Caovilla HH. Treatment of Dizziness and Vertigo in Children. In A Cesarani, D Alpini (eds), *Diagnosi e Tratamento dei Disturbi dell'Equilibrio nell età evolutiva ed involutiva*. Verona: Bi & Gi, 1991:83–92.
23. Ganança MM, Mangabeira Albernaz PL, Caovilla HH. The Efficacy of Clonazepam in the Treatment of Vertigo, Nausea and Tinnitus in Cardio-Vascular Diseases. In CF Claussen, MV Kirtane (eds), *Vertigo in Cardiovascular Diseases*. Amsterdam: Excerpta Medica, 1986:479–483.
24. Ganança MM, Mangabeira Albernaz PL, Caovilla HH, Ganança, FF. Drug Therapy of Dizziness, Hypoacusia and Tinnitus due to Neurotological Disorders. In CF Claussen, MV Kirtane, D Schneider (eds), *Vertigo, Hypoacusia and Tinnitus Due to Central Disequilibrium*. Hamburg: medicin + pharmacie Dr. Werner Rudat & Co., Nachfolger, 1994:617–623.
25. Ganança MM, Mangabeira Albernaz PL, Dirckensen M, et al. A ação antivertiginosa do clonazepam. *Arq Bras Med* 57:97–102; 1983.
26. Ganança MM, Mangabeira Albernaz PL, Caovilla HH, et al. Oito anos de experiência clínica com clonazepam no tratamento da vertigem. *A Folha Médica* 89:237–246, 1984.
27. Ganança MM, Mangabeira Albernaz PL, Caovilla HH, et al. Comparative study of the effects of clonazepam and cinnarizine in the treatment of vestibular diseases. In *Proceedings of the International Symposium on Ophtalmo-Neuro-Otology*. Budapest: Hungarian Oto-Rhino-Laryngological Society, 1985:320–322.
28. Mangabeira Albernaz PL, Ganança MM, Fonseca MC. Clonazepam no tratamento dos distúrbios otoneurológicos. *A Folha Médica* 88:283–287, 1984.
29. Ganança MM, Mangabeira Albernaz PL, et al. The Antivertiginous Action of Clonazepam. In CF Claussen, MV Kirtane (eds), *Basics of Neurootology and Applied Neurootological Diagnosis in Presbyvertigo, Presbyataxia and Presbytinnitus*. Hamburg: medicin + pharmacie Dr. Werner Rudat & Co., Nachfolger, 1988:401–413.
30. Ganança MM, Caovilla HH. A Survey of Modern Drug Treatment in Presbyvertigo and Presbyataxia. In A Cesarani, D Alpini (eds), *Diagnosi e Tratamento dei Disturbi dell'Equilibrio nelletà evolutiva ed involutiva*. Verona: Bi & Gi, 1991:237–250.
31. Johnson GD. Medical management of migraine-related dizziness and vertigo. *Laryngoscope* 108(suppl 85):1–28, 1998.
32. Brookes GB. The pharmacological treatment of Ménière's disease. *Clin Otolaryngol* 21:3–11, 1996.