

# Betahistine Effects on Tinnitus in Patients with Meniere’s Disease

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## Introduction

Meniere’s is a fluctuating disease with an unpredictable natural course. These characteristics raise challenges in investigating and comparing treatment modalities for this disease. The goal of treatment of Meniere’s disease is to prevent the severity and number of attacks, prevent progression of disease, reduce and eliminate tinnitus and hearing loss, and alleviate chronic symptoms. In a 2000 review of 154 publications on medical treatment of Meniere’s disease, Claes and Heyning concluded that only diuretics and betahistine have proven efficacy for long-term control of vertigo. Their conclusion does not include the more recent clinical trials assessing the efficacy of symptom control with transtympanic injections (chemical labyrinthotomy). Chemical labyrinthotomy with steroids and aminoglycosides, endolymphatic sac decompression and shunting, vestibular nerve section, and labyrinthectomy are less conservative measures used to manage patients who are resistant to conservative therapy.

Endolymphatic hydrops is the proposed etiology for Meniere’s disease, however a causal relationship has yet to be proven. It is suggested that in some circumstances cochlear vascular insufficiency may be the cause of increased endolymphatic pressure in the inner ear and endolymphatic hydrops. Betahistine, a partial histamine H1 receptor agonist and potent H3 receptor antagonist, has been used in the management of Meniere’s disease for several decades. This drug is widely used in Canada, Europe, Latin America, and other parts of the world however it is not approved by the Food and Drug Administration. In addition to its effects on histamine neurotransmission, it is believed to increase inner ear and intracranial blood flow, inhibit neuronal activity in the medial and lateral vestibular nuclei, and effect behavioral adaptation through its effects on the histamine H3 receptors involved in vestibular compensation. In animal models betahistine has been demonstrated to antagonize the local H3 receptors in the inner ear and increase cochlear and posterior semicircular ampullary blood flow. This mechanism of action of betahistine may be the key in management of inner ear hydrops and control of Meniere’s symptoms.

Variable outcomes have been reported in symptom control in patients with Meniere’s disease treated with betahistine. Many trials and retrospective analyses suggest a good control on vertiginous symptoms however outcomes vary on control of tinnitus, hearing loss, and aural fullness. The goal of this study is to assess the effects of betahistine on tinnitus in patients with Meniere’s disease.

## Methods and Materials

A Retrospective review of all Meniere’s disease patients treated with betahistine from January 2001 to January 2004 at our institution was performed. Patients were diagnosed and classified with Meniere’s disease based on the 1995 Academy of Otolaryngology-Head and Neck Surgery diagnostic guidelines. Patients included in this study received therapy with 8-64mg/day of betahistine. A waiver form was signed by all patients prior to use of betahistine because of its off label use.

Patient charts were reviewed for analysis of symptom control. Patients were also contacted by phone or email and questioned on the effects of betahistine on their Meniere’s symptoms. Patients were introduced to a 5 point tinnitus improvement scale ranging from 1 (=complete response) to 5 (=no response). A score of 2 represented a very good response, 3 a good response, and 4 a mild response. A score of 1-3 was considered a clinically significant improvement in tinnitus. A scale was not provided to the patients for vertigo, hearing loss, and aural fullness assessment.

## Results

A total of 764 patients with Meniere’s disease were identified in our electronic database. Fifty of these patients were treated with betahistine for vestibular symptoms. Duration of therapy varied from several doses to 4 years. Thirty patients were successfully contacted for a phone interview or via email. Of the thirty patients, 26 patients had definite Meniere’s and 4 patients had possible Meniere’s based on the 1995 AAO-HNS diagnostic criteria. A patient was excluded from the study as she had to stop betahistine immediately secondary to the onset of palpitations after the first several doses. Twenty six of the 29 patients included in the study reported tinnitus as a symptoms. Only 16 of the 26 reported tinnitus as a disturbing symptom. A clinically significant reduction in tinnitus (score of 1-3 on the tinnitus scale) was seen in 7 of the 26 patients (27%). Tinnitus was significantly reduced in 6 of the 16 patients (37.5%) reporting tinnitus as a disturbing symptom. Adverse events included headaches, nausea, and dyspepsia in 1 patient and increased dizziness, headaches, and nausea in another. One patient developed palpitations after the first several doses and stopped the medication immediately. Another patient briefly stopped taking betahistine as she required inhalers to treat bronchitis. Elevated liver function tests were seen in another patient after several weeks of therapy.

Table 1. Results

Number of subjects classified in each Meniere’s Disease category based on 1995 American Academy of Otolaryngology guidelines:	
Certain Meniere’s Disease	0
Definite Meniere’s Disease	25
Probable Meniere’s Disease	0
Possible Meniere’s Disease	4

Table 2. Results

A total of 29 patients with Meniere’s Disease treated with Betahistine are retrospectively analyzed	
<u>Symptoms</u>	
Vertigo/Dizziness	100% (29/29)
Tinnitus	90% (26/29)
Aural Fullness	72% (21/29)
Hearing Loss	86% (25/29)
<u>Symptom response to Betahistine</u>	
Vertigo	69% (20/29)
Tinnitus	27% (7/26)
Aural Fullness	19% (4/21)
Hearing Loss	16% (4/25)

Table 3. Results

	Number of patients	% with a clinical significant response to Betahistine
Patients with tinnitus	26	27% (7/26)
Patients adversely affected by their tinnitus	16	37.5% (6/16)

## Discussion

Betahistine is a histamine analogue that has been widely used for the treatment of Meniere’s disease and vestibular disorders around the world. It was first introduced to the market in Canada in 1968. As of December 2005 this drug has been approved in >80 countries and administered to over 130 million patients. Betahistine does not have FDA approval. The most common adverse event reported is cutaneous hypersensitivity reactions.

Most clinical trials and retrospective reviews demonstrate clinical improvement in vertigo in patients with Meniere’s disease and vestibular disorders treated with betahistine. Over 2/3 of our patients treated with betahistine also had significant improvement in their dizziness and vertigo.

The results and efficacy of betahistine effects on tinnitus treatment varies amongst different reports. In 1966 Elia et al. published one of the first studies that demonstrated improvement in tinnitus in patient with Meniere’s disease treated with betahistine. In 1984 Salami et al. reported reduction of vertigo, aural fullness, and tinnitus in Meniere’s patients treated with betahistine but no improvement in hearing loss. In 2000 Bardoo et al. reported that out of 15 patients with tinnitus, 7, 1, and 0 patients had tinnitus 1, 2, and 3 weeks after initiation of therapy. In 2011 Gananca et al. reported tinnitus improvement in 30.5% of patients with vestibular disorders treated with betahistine relative to 17.1% of the control group. Our clinical response rate of 27% in patients with tinnitus is comparable to the 30.5% improvement noted by Gananca et al, although 37% of patients disturbed by their tinnitus in our study had a significant response to therapy. In a double blind 16 week cross-over trial on 35 patients with Meniere’s treated with betahistine reported by Schmidt et al. in 1992, no improvement in tinnitus, aural fullness, or hearing loss was seen. Additional publications also demonstrate lack of tinnitus control with betahisitne therapy in Meniere’s disease patients.

Large-scale double blind trials for the effects of betahistine on Meniere’s symptoms including tinnitus would be the ideal research design however the unpredictable natural course of this disease still inflicts challenges on interpretation of data. We advocate efforts to obtain FDA approval for betahistine therapy in Meniere’s disease patients based on the available literature support for this drug and with an overall noted acceptable safety profile.

## Conclusions

Betahistine therapy can reduce vertigo and dizziness symptoms in over 2/3 of patients with Meniere’s disease. Tinnitus is less responsive to betahistine therapy however still may resolve or improve significantly in over 1/3 of patients with Meniere’s disease disturbed by their tinnitus.

## Abstract

Objectives: Analyzing the effects of betahistine on tinnitus in patients with Meniere’s disease.

Methods: Retrospective review of the effects of betahistine on tinnitus in patients with Meniere’s disease treated from 01/2010-01/2014. Patients included in this study received therapy with 8-64mg/day of betahistine. Clinical improvement in tinnitus symptoms was defined as a partial or total response.

Results: A total of 764 patients with Meniere’s disease were identified in our electronic database. Fifty of these patients were treated with betahistine for vestibular symptoms. Duration of therapy varied from several doses to 4 years. Thirty patients were successfully contacted for a phone interview or via email. Twenty six patients reported tinnitus as a symptom. Only 16 of the 26 reported tinnitus as a disturbing symptom. Seven of the 26 patients had clinical improvement of their tinnitus (27%). Twenty of the 29 patients reported improvement in their vestibular symptoms (20/29: 69%).

Conclusion: Betahistine reduces vertigo and tinnitus symptoms in Meniere’s patients. The effect on vertigo control is more clinically significant.

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