

Intratympanic Gentamicin for Intractable Ménière's Disease – A Review and Analysis of Audiovestibular Impact

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Abstract

Introduction Intratympanic gentamicin regulates the symptoms in most patients with incapacitating Ménière's disease. The treatment protocols have changed over the years from medical labyrinthectomy to preservation of vestibular function.

Objectives This study aims to review the audiovestibular response related to the effect of the drug in controlling vertigo.

Data Synthesis Articles were identified by means of a search in the PubMed database using the key words *Meniere* and *intratympanic or transtympanic gentamicin*. Total 144 articles were reviewed after excluding those that were technical reports, those based on experimental animal studies, those that focused on outcomes other than vertigo (tinnitus or aural fullness), those with delivery methods other than tympanic membrane injection, and those with bilateral cases. If there was more than one article by the same author(s) or institution, only the most recent one matching the aforementioned criteria and those that were not overlapping were included.

Conclusion Titration methods or multiple injections on a daily basis can be preferred if the patients have profound or non-serviceable hearing, since these methods have significant incidence of hearing loss. Treatment protocols with a frequency of injection not shorter than once a week, or those with injections on a monthly basis as "needed" provide the same level of vertigo control with better preservation of hearing. Caloric testing is not an ideal tool to analyze the correlation between vertigo control and the effect of gentamicin as compared with gain asymmetry of the vestibulo-ocular reflex. Vestibular-evoked myogenic potentials and the head thrust test are more reliable than other vestibular tests for the follow-up of patients undergoing gentamicin treatment.

Keywords

- ▶ Ménière's disease
- ▶ intratympanic gentamicin
- ▶ vertigo

Introduction

Ménière's disease is characterized by episodic vertigo, tinnitus, aural fullness and fluctuating hearing loss. The treatment of patients with Ménière's disease is usually directed at the most disabling symptom, which is incapacitating vertigo. Medical therapy usually regulates the symptoms in most patients with this disease. Surgical intervention or intratympanic gentamicin is offered to those who are resistant to the

medical therapy, which, ideally, should control the vertigo while preserving the hearing level and balance. The side effects of gentamicin are well-known. The risks of vestibular and cochlear toxicity are related to the duration of the therapy, the total or cumulative dose, exposure, individual susceptibility, renal function, the patient's age, and associated inner ear problems, like noise exposure, autoimmune disorders etc. Intratympanic gentamicin for the treatment of severe vertigo was reported by Lange.¹ The initial approach

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Table 1 Comparison of vertigo control and hearing loss in studies using gentamicin at frequent intervals

Study	Date	Patients	Injection or titration	Hearing loss	Vertigo control
Möller et al ²	1988	15	3–11 days injection	5 (33.4%)	14 (93.4%)
Laitakari ³	1990	20	3 days injection	9 (45%)	18 (90%)
Parnes et al ⁴	1993	12	3 times titration daily for 4 days	5 (41.7%)	12 (100%)
Murofushi et al ⁵	1997	18	3–5 days injection	6 (30%)	14 (77.8%)
Corsten et al ⁶	1997	21	3 times titration daily for 4 days	12 (57%)	17 (80.9%)
Rauch et al ⁷	1997	21	Twice daily–twice weekly	5 (24%)	20 (95%)
Kaplan et al ⁸	2002	90	3 times titration daily for 4 days	22 (25.6%)	84 (93.4%)

was complete vestibular ablation to control the vertigo. However, with this approach, the hearing was at a greatest risk. Over the decades, several modifications have emerged regarding the concentration of the gentamicin solution, the frequency of injections and the method of delivery. This study aims to review the audiovestibular response related to the effect of the drug to control the vertigo and the protocols that are necessarily modified over the years from “medical labyrinthectomy” or “chemical labyrinthectomy” to preservation of vestibular function.

Review of the Literature

A review of the literature on the audiovestibular impact of intratympanic gentamicin for intractable unilateral Ménière's disease was conducted, with data extracted only from articles written in English. The articles were identified by means of a search in the PubMed database using the keywords *Meniere* and *intratympanic or transtympanic gentamicin*, which yielded 205 articles. Total 144 articles were reviewed for the study after we excluded those that were technical reports, those based on experimental animal studies, those that focused on outcomes other than vertigo (tinnitus or aural fullness), those with delivery methods other than tympanic membrane injection, and those with bilateral cases. Comparative studies (intratympanic gentamicin versus sac surgery or medical therapy etc.) were included if the outcome measures for the effect of gentamicin were clear. The search only included articles published between 1989 and 2015. If there was more than one article by the same author(s) or institution, only the most recent one matching the aforementioned criteria and those that were not overlapping were included. The studies were classified into two main groups: hearing monitoring and signs of vestibular impact. The first group was sub classified into three groups: pure tone audiogram and speech discrimination; electrocochleography; and otoacoustic emission. The second group was sub classified into eight groups: spontaneous and head-shaking nystagmus; caloric response; head thrust test; subjective visual vertical; vestibular-evoked myogenic potentials; dynamic visual acuity; posturography; and rotatory chair for comparative review in terms of the audiovestibular impact of intratympanic gentamicin.

Discussion

I. Hearing monitoring after gentamicin

a. *Pure tone audiogram, speech discrimination score.* The impact of intratympanic gentamicin on hearing is not predictable. The extent of the damage throughout the dark cells and hair cells will determine the outcome, which eventually depends on the concentration of gentamicin, its penetrance through the round window and, most of all, the frequency of application, since the clearance of gentamicin from the inner ear takes days after a single injection. The hearing will probably not change in some patients. Some will show a certain degree of improvement, while others will show the opposite. Studies reporting comparative analyses of mean pure tone averages before and after intratympanic gentamicin in groups of patients do not help to understand the risk of a specific treatment protocol for the hearing. Therefore, it is more important to focus on the number of patients with more than 10 dB of hearing loss after the gentamicin treatment.

Studies indicate that follow-up until the first signs of vestibular ablation, like motion intolerance, ataxia etc. by monitoring the hearing with pure tone threshold, speech reception threshold and word discrimination score only is risky due to the cumulative effect of the drug if a daily injection or titration methods have been used (– **Table 1**). In earlier studies, the highest rate of vertigo control was reported with daily injections or multiple titrations. On the other hand, considerable hearing loss was experienced in several studies. Möller et al treated 15 patients with disabling Ménière's disease with daily injections for periods ranging from 3 to 11 days.² They achieved 93.4% of vertigo control, but also 33.4% of hearing loss. They reported that none of the patients were responsive to caloric stimulation. Laitakari reported 90% of vertigo control and 45% of hearing loss in 20 patients who had daily intratympanic gentamicin for a minimum of 3 consecutive days.³ Parnes et al reported 41.7% worsening of the hearing in their group of patients who received 3 daily injections for 4 days.⁴ Murofushi et al, using several daily injections, reported hearing loss in 30% of cases.⁵ Corsten et al reported 80.9% of vertigo control, but

57% of hearing loss in 21 patients who had gentamicin instillation 3 times a day for 4 days.⁶ Rauch and Oas reported 95% of vertigo control and 24% of hearing loss in 21 patients.⁷ Kaplan et al reviewed the 10-year long-term results of 114 patients treated with gentamicin instillation 3 times a day for 4 consecutive days. They achieved 93.4% of vertigo control and 25.6% of hearing loss.⁸ In early 2000's, regarding patients with hearing deterioration and even those becoming deaf, there was a discussion about reducing the gentamicin dose or performing the application at longer intervals. Daily titration methods were abandoned. Transtympanic gentamicin therapy was modified to weekly intervals as "needed" or "on demand" to reduce the symptoms of Ménière's disease, aiming to maintain cochlear as well as vestibular function (► **Table 2**). Harner et al reported a very high rate of vertigo control with preservation of hearing in 43 patients.⁹ There were no patients with changes in cochlear function and ablation of the labyrinth. All patients received one injection, and half of them received a repeat injection one month after therapy. Minor used gentamicin on weekly intervals until the development of spontaneous nystagmus, head-shaking nystagmus or head thrust sign. Vertigo was controlled in 91% of the patients, and profound hearing loss only occurred in 1 patient.¹⁰ Atlas et al reviewed the outcomes of 83 patients who received weekly injections. They reported hearing loss in 17% of the patients, with vertigo control in 84%.¹¹ Martin and Perez reported vertigo control in 83.1% of the patients, and hearing loss in 15.5% of them after gentamicin at weekly intervals.¹² Flanagan et al reported 21.4% of hearing loss and 81.3% of vertigo control after a single injection of gentamicin,¹³ and De Beer et al reported 15.8% of hearing loss and 80.7% of vertigo control after between 1 and 10 intratympanic injections at a minimum interval of 27 days.¹⁴ Casani et al reported 12% of hearing loss after a maximum of 2 injections of gentamicin, and 81% vertigo control.¹⁵

b. *Electrocochleography*. The summating potential and action potential (SP/AP) ratio of the eighth nerve has been used for the diagnosis of Ménière's disease. The enlarged summating potential supports the presence of the endolymphatic hydrops. Gentamicin affects both sensorial and secretory cells of the inner ear. Hearing improve-

ment in some patients undergoing gentamicin treatment can be explained by the reduction in the endolymphatic hydrops. Adamanis et al reviewed electrocochleography in Ménière's patients undergoing gentamicin therapy and reported a statistically significant reduction in the SP/AP ratio. This finding supported the hypothesis that gentamicin improves the electrophysiological function of the cochlea in some patients.¹⁶ However, the beneficial effect of gentamicin does not depend on the improvement of the SP/AP ratio, and vertigo control can be achieved without any change in electrocochleography.¹⁷

c. *Otoacoustic emission*. Otoacoustic emissions can be used to detect any cochlear changes due to intratympanic gentamicin before the audiometric loss.¹⁸ However, the test has some limitations. The hearing level of the patients before the gentamicin treatment should be better than 40 dB.

II. Signs of vestibular impact

a. *Spontaneous and head-shaking nystagmus*. Repetitive injection of gentamicin until the patients develop spontaneous nystagmus or post-head-shaking nystagmus that was not present before may confirm that the injection is effective. Fast-phase nystagmus toward the unaffected healthy ear is an evident sign of decreased labyrinthine function.³ But, in this case, the hearing could be in danger, and should be preserved before the ablation of the vestibular system. On the other hand, Parnes et al reported irritative spontaneous nystagmus that is fast component directed toward the affected ear. The authors state that this is a unique finding that may represent a recovery phenomenon resulting from a temporary reversible ototoxic effect in the treated ear. However, this sign was only evident in 3 patients (25%) in their series.⁴ It seems that when this sign is absent, other early clues of vestibular involvement, like head-shaking nystagmus and head thrust sign, should be considered. Casani et al reported that these signs could be obtained within days after only 1 injection in 81% of patients.¹⁹

b. *Caloric response*. Most patients with Ménière's disease may already have reduced the caloric response on the affected side. A decrease in the caloric response is eventually expected after intratympanic gentamicin injections. However, the absence of response to caloric stimulation after the completion of the gentamicin therapy demonstrates acute vestibular deafferentation that is permanent. Yetiser

Table 2 Comparison of vertigo control and hearing loss in studies using gentamicin at weekly or monthly basis as needed

Study	Date	Patients	Injections	Hearing loss	Vertigo control
Harner et al ⁹	1998	43	1 injection, another one 1 month later	None	43 (100%)
Minor ¹⁰	1999	34	Weekly interval until certain signs	1 (3%)	28 (91%)
Atlas et al ¹¹	1999	83	Weekly interval (maximum of 4)	14 (17%)	70 (84%)
Martin et al ¹²	2003	71	Weekly	11 (15.5%)	59 (83.1%)
Flanagan et al ¹³	2006	56	One injection	12 (21.4%)	46 (81.3%)
De Beer et al ¹⁴	2007	57	27 days minimum	9 (15.8%)	46 (80.7%)
Casani et al ¹⁵	2012	32	Weekly (maximum of 2)	4 (12%)	26 (81%)

et al, who gave 3 gentamicin injections for the 3 consecutive days, followed-up their patients after treatment with caloric testing for 6 months and found a constant increase in the number of patients having caloric weakness or inexcitability up to 2 weeks.²⁰ Murofushi et al, who gave multiple injections, concluded that the patients with abolished caloric response had chronic vestibular insufficiency that was not less than those after vestibular neurectomy or surgical labyrinthectomy.⁶ Therefore, the aim of the gentamicin therapy should be the control of the vertigo with preservation of the caloric response.

- c. *Head thrust test.* Gentamicin therapy is associated with vestibulo-ocular reflex deficit, which is evident during rapid head movements.²¹ It is a useful prognostic indicator, even after a single intratympanic gentamicin injection.^{19,22} Cerchiai et al compared the follow-up of patients undergoing the conservative treatment and the follow-up of those undergoing gentamicin injections. It has been reported that the high-frequency vestibulo-oculomotor reflex is preserved even in late stages of Ménière's disease. Therefore, a positive head thrust test is a reliable sign of the effect of the gentamicin treatment.²³
- d. *Subjective visual horizontal.* The measurement of the subjective visual horizontal and the body tilt is easy to perform, and it can be repeated on a daily basis as a monitor for the vestibular effect of gentamicin. A significant reduction in the perception of the head and body tilt in the gentamicin-treated side was found to be correlated with the loss of caloric response.²⁴ Tribukait et al reported that a significant asymmetry in the roll-tilt perception was evident even in the long-term. However, the authors also stated that the lack of correlation between the degree of subjective visual horizontal in the upright position and the roll-tilt perception (body position at 10, 20 and 30 degrees of tilt to the right and left) suggested that these parameters were dependent on different afferent inputs (vestibulo-collic etc.). Another interesting point regarding the recovery of the subjective visual horizontal after intratympanic gentamicin treatment is that it is not predictable. However, recovery takes longer than the disappearance of the spontaneous nystagmus, and patients with normal vestibular-evoked myogenic potentials before the therapy usually have a tendency to experience a delay in recovery.²⁵
- e. *Vestibular-evoked myogenic potentials.* Picciotti et al reported that all normal vestibular-evoked myogenic potential responses disappeared after the gentamicin treatment in their series, the caloric response was absent in 50%, and caloric test-induced asymmetry was observed in the remaining patients.²⁶ Gode et al analyzed vestibular-evoked myogenic potentials and caloric test after a single-shot low-dose gentamicin treatment at the 2nd week in 25 patients. Vestibular-evoked myogenic potentials were absent in 68% and distorted in 8% of the patients. The predictive role of vestibular-evoked myogenic potentials in post-treatment dizziness and vertigo control was more reliable than the caloric test.²⁷

- f. *Dynamic visual acuity.* Compensatory eye movement in response to linear acceleration of the head, opposite in direction to the head movement, is generated to stabilize the image on the target. Thus, the balance is maintained during high-velocity head motion. The impact of the peripheral vestibulopathy on the vestibular-ocular reflex is associated with the inability to have a clear image of the target on the retina, resulting in visual blurring with head motion. The dynamic visual acuity test provides indirect information about the vestibulo-ocular reflex by way of the subject's ability to see during rapid head motion.²⁸ This test provides valuable information about the degree of vestibulopathy in patients with Ménière's disease. However, its predictive role on the intratympanic gentamicin treatment has not been documented.
- g. *Posturography.* The dynamic nature of Ménière's disease may prevent the development of central compensation. Pyykkö et al evaluated the postural compensation with posturography in 93 patients treated with intratympanic gentamicin.²⁹ In two years of follow-up, they found a significant improvement in postural stability, mostly due to the absence of attacks. It seems that posturography is a tool that is more useful to show compensation after gentamicin treatment than trying to monitor the efficacy of the treatment.²⁶
- h. *Rotatory chair.* Perez and Rama-Lopez found that the vestibulo-ocular reflex after rotation toward the treated side and the gain in the sinusoidal harmonic acceleration test were significantly reduced after the intratympanic gentamicin treatment.³⁰ However, the predictive role of the rotatory chair test on the efficacy of the intratympanic gentamicin treatment is low.

Final Comments

In conclusion, the inner ear toxicity of gentamicin follows an order. Secretory dark cells of the vestibule are the first to be damaged, followed by the vestibular neuroepithelium and, finally, the hair cells of the organ of Corti are destroyed. The dose in each application and the time interval between two doses are two critical issues to be solved. It is likely that the initial reversible effect of gentamicin on both the vestibule and cochlea turns eventually to an irreversible stage due to the accumulation of consecutive doses in the inner ear because of the slow clearance of gentamicin. We cannot manipulate the amount of gentamicin in the inner ear, which is apparently related to several conditions, like round window penetration, tubal patency, histology of the middle ear mucosa etc. However, we can conduct the whole treatment by manipulating the frequency of injections, always considering the vestibular and audiological signs. Titration methods or multiple injections on a daily basis can be preferred if the patients have profound or non-serviceable hearing, since these methods have significant incidence of hearing loss.³¹ Treatment protocols with a frequency of injections not shorter than once a week or those with injections on a monthly basis as "needed" provide the same level of vertigo control with better preservation of hearing.³²

The caloric test is a good indicator of loss of function in patients with Ménière's disease. However, the aim of the intratympanic gentamicin treatment should not be the complete ablation of the vestibular function with absence of caloric response. Besides, caloric testing is not an ideal tool to analyze the correlation between vertigo control and the effect of gentamicin as compared with gain asymmetry of the vestibulo-ocular reflex.³³ Vestibular-evoked myogenic potentials and the head thrust test are more reliable than other vestibular tests for the follow-up of patients receiving gentamicin treatment.

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