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.

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. The initial approach
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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Patients</th>
<th>Injection or titration</th>
<th>Hearing loss</th>
<th>Vertigo control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Möller et al2</td>
<td>1988</td>
<td>15</td>
<td>3–11 days injection</td>
<td>5 (33.4%)</td>
<td>14 (93.4%)</td>
</tr>
<tr>
<td>Laitakari3</td>
<td>1990</td>
<td>20</td>
<td>3 days injection</td>
<td>9 (45%)</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>Parnes et al4</td>
<td>1993</td>
<td>12</td>
<td>3 times titration daily for 4 days</td>
<td>5 (41.7%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Murofushi et al5</td>
<td>1997</td>
<td>18</td>
<td>3–5 days injection</td>
<td>6 (30%)</td>
<td>14 (77.8%)</td>
</tr>
<tr>
<td>Corsten et al6</td>
<td>1997</td>
<td>21</td>
<td>3 times titration daily for 4 days</td>
<td>12 (57%)</td>
<td>17 (80.9%)</td>
</tr>
<tr>
<td>Rauch et al7</td>
<td>1997</td>
<td>21</td>
<td>Twice daily–twice weekly</td>
<td>5 (24%)</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>Kaplan et al8</td>
<td>2002</td>
<td>90</td>
<td>3 times titration daily for 4 days</td>
<td>22 (25.6%)</td>
<td>84 (93.4%)</td>
</tr>
</tbody>
</table>

**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 method 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. 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. Parnes et al reported 41.7% worsening of the hearing in their group of patients who received 3 daily injections for 4 days. Murofushi et al, using several daily injections, reported hearing loss in 30% of cases. Corsten et al reported 80.9% of vertigo control, but...
Table 2 Comparison of vertigo control and hearing loss in studies using gentamicin at weekly or monthly basis as needed

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Patients</th>
<th>Injections</th>
<th>Hearing loss</th>
<th>Vertigo control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harner et al</td>
<td>1998</td>
<td>43</td>
<td>1 injection, another one 1 month later</td>
<td>None</td>
<td>43 (100%)</td>
</tr>
<tr>
<td>Minor</td>
<td>1999</td>
<td>34</td>
<td>Weekly interval until certain signs</td>
<td>1 (3%)</td>
<td>28 (91%)</td>
</tr>
<tr>
<td>Atlas et al</td>
<td>1999</td>
<td>83</td>
<td>Weekly interval (maximum of 4)</td>
<td>14 (17%)</td>
<td>70 (84%)</td>
</tr>
<tr>
<td>Martin et al</td>
<td>2003</td>
<td>71</td>
<td>Weekly</td>
<td>11 (15.5%)</td>
<td>59 (83.1%)</td>
</tr>
<tr>
<td>Flanagan et al</td>
<td>2006</td>
<td>56</td>
<td>One injection</td>
<td>12 (21.4%)</td>
<td>46 (81.3%)</td>
</tr>
<tr>
<td>De Beer et al</td>
<td>2007</td>
<td>57</td>
<td>27 days minimum</td>
<td>9 (15.8%)</td>
<td>46 (80.7%)</td>
</tr>
<tr>
<td>Casani et al</td>
<td>2012</td>
<td>32</td>
<td>Weekly (maximum of 2)</td>
<td>4 (12%)</td>
<td>26 (81%)</td>
</tr>
</tbody>
</table>
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. Murofushi et al, who gave
multiple injections, concluded that the patients with abol-
ished caloric response had chronic vestibular insufficiency
that was not less than those after vestibular neurectomy or
surgical labyrinthectomy. Therefore, the aim of the gen-
tamicin 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. It is a useful prognostic indicator,
even after a single intratympanic gentamicin injec-
tion. 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.

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 signi-
ficant 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. 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-colic etc.). Another
interesting point regarding the recovery of the subjective
visual horizontal after intratympanic gentamicin treat-
ment is that it is not predictable. However, recovery takes
longer than the disappearance of the spontaneous nys-
tagmus, and patients with normal vestibular-evoked
myogenic potentials before the therapy usually have a
tendency to experience a delay in recovery.

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. Gode et al ana-
lyzed 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 myo-
genic potentials in post-treatment dizziness and vertigo
control was more reliable than the caloric test.

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. This test provides valuable information about
the degree of vestibulopathy in patients with Ménière’s
disease. However, its predictive role on the intratympa-
nic 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. 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.

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. However, the predictive role of
the rotatory chair test on the efficacy of the intratym-
panic 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 penetrance,
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
audiologic 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. Treatment protocols with a fre-
quency 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.22
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. 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.

References