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Main Article

Outcomes in the use of intra-tympanic gentamicin in the treatment of Ménière's disease

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Abstract

The pathogenesis of Ménière's disease is associated with a disorder of ionic homeostasis, with the pathologic correlate being endolymphatic hydrops. Despite uncertainty as to its particular mode of action, it is accepted wisdom that intra-tympanic gentamicin has a definite therapeutic role in the control of symptoms in patients who fail to respond to medical therapy. This study reports an evaluation of the efficacy of intra-tympanic gentamicin in the treatment of Ménière's disease and also presents a simple, reliable, safe method of administering gentamicin for this purpose.

A retrospective review of 56 patients undergoing intra-tympanic gentamicin treatment for Ménière's disease was conducted. Response to treatment was analysed using a patient survey and examination of pure-tone averages. An overall significant improvement in vertigo symptoms of 81.3 per cent was found. There was a 21.4 per cent rate of significant hearing loss, defined as greater than 10 dB, with an average loss in this group of 18.5 dB. A single dose of gentamicin applied directly to the round window resulted in a high rate of control of vertigo, with acceptably low rates of hearing loss.

Key words: Ménière's Disease; Gentamicin; Middle Ear; Round Window

Introduction

Ménière's disease is a disorder of the inner ear inferred by the presence of fluctuating hearing loss, episodic vertigo, tinnitus and aural fullness. Abnormalities in the homeostasis of fluid and electrolytes are associated with the pathologic correlate of endolymphatic hydrops.

Despite uncertainty as to its particular mode of action, it is accepted wisdom that intra-tympanic gentamicin has a definite therapeutic role in the control of episodic vertigo in those who fail to respond to medical therapy for Ménière's disease.

There have been several proposed regimens for the delivery, dose and the number of procedures required to adequately control the symptoms of Ménière's disease while minimizing hearing loss. Analysis by Blakley[1] and Diamond[2] failed to find a significant difference in the results of any particular regime. Much recent literature has espoused the utility of a titration regime to maximize vertigo control and to minimize the risks of significant hearing loss.[2]

In the assessment and preparation of patients with Ménière's disease it is customary to perform caloric vestibular function tests and to use changes in responsiveness as one of the guides to success or termination of therapy. Two factors minimize the utility of this approach. The first is the commonly observed situation in which sensitivity to physiologic head movements is maintained irrespective of caloric test response. Additionally, while the control of vertigo is associated with a reduction in unilateral vestibular function, ablation is not required, and thus there is no benefit in following therapy with caloric testing, compared with follow-up clinical assessment.

This study reviews the efficacy of two proposed protocols for administering intra-tympanic gentamicin in the management of Ménière's disease.

Materials and methods

Fifty-six patients who underwent intra-tympanic gentamicin therapy for Ménière's disease at St Vincent's Hospital, Sydney, Australia, were retrospectively studied (Table I). All procedures were conducted by the senior author of the paper. Prior to selection for this therapy, all patients underwent a

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complete neuro-otologic examination with pure-tone audiometry and full vestibular studies; retrocochlear pathology was excluded via magnetic resonance imaging (MRI) studies.

The procedures were carried out over a period from November 1999 to July 2002. The technique employed for the first 21 patients (November 1999 to March 2000) involved raising a tympanomeatal flap and inspecting and clearing the round window niche, with placement of a piece of gelfoam. Four milligrammes of gentamicin (0.1 ml of a 40 mg/ml solution) was then injected onto the gelfoam. A T-tube was left in contact with the gelfoam. Further doses of gentamicin were given at weekly intervals in the first six cases.

Commencing March 2000, an alternate technique was employed in the remaining 35 patients. This involved raising a tympanomeatal flap and inspecting and clearing the round window niche. A piece of gelfoam was placed to which 4 mg of gentamicin was subsequently added, and the flap replaced. Eleven patients had a second procedure, two on the contralateral ear. Three patients underwent vestibular nerve section (VNS) within six months of their gentamicin therapy. Eight patients were noted to have bilateral disease during the period of the study, of whom two received treatment in each ear. Twelve patients had previously undergone other surgical procedures for the treatment of their Ménière's disease, including one attempted nerve section.

Pre- and post-operative pure-tone averages (PTAs) were reviewed, using the American Association of Otolaryngology – Head and Neck Surgery (AAO-HNS) criteria.[3] A questionnaire was then forwarded to all patients. Symptoms of vertigo, hearing, fullness, pressure and tinnitus were evaluated. A modification of the AAO-HNS criteria for reporting of vertigo control was used.[3] Response was graded as better, same or worse, at zero to six months, six to 12 months and 18 to 24 months following surgery; symptoms were also assessed six months prior to surgery. Patients' PTAs were calculated according to the AAO-HNS criteria, averaging thresholds at 500, 1000, 2000 and 3000 Hz.

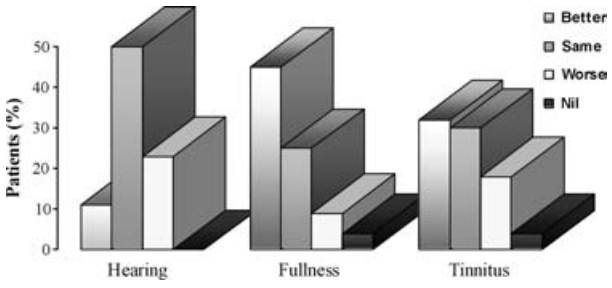

FIG. 1

Post-operative change in symptoms. In 59% of patients, hearing remained unchanged or improved, while 21% worsened (in 20% data were unavailable). In 45% of patients, the sensation of fullness improved, while 32% experienced a reduction in tinnitus.

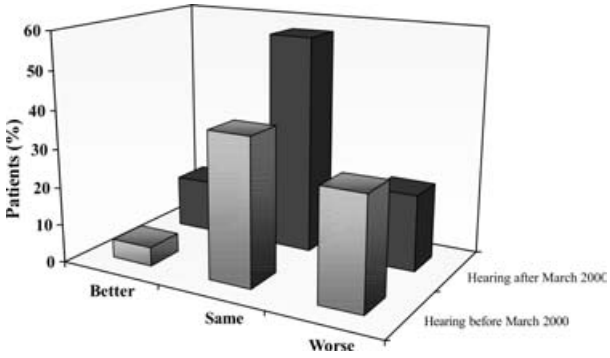

FIG. 2

Comparison of hearing results achieved following two different modes of administration of gentamicin employed before and after March 2000. (See methods.) The figure shows that the later technique appeared to produce better results.

Results

There was an 89 per cent (50/56) response rate to the survey, from which the average period of follow up was established as 19.1 months (range: 2–40 months). A total of 50 patients underwent 61 procedures. Complete resolution of vertigo at the longest period of follow up for each patient was found in 43.8 per cent (21/48). An improvement in vertigo attacks of between one to three categories was noted in five patients. Twelve patients experienced significant improvement in either the number and/or the severity of attacks, while still remaining within the 1–40 per month attack range. Four patients reported no change in symptoms, with two proceeding to VNS. Worsening of symptoms was reported by three respondents, one of whom underwent VNS (Table II). An overall significant improvement in the vertigo symptoms of 39/48 (81.3 per cent) patients was found, with no significant improvement in 4/48 (8.3 per cent) and progression of symptoms reported in 3/48 (6.3 per cent).

Pure dizziness as the primary symptom was noted by two patients, both of whom reported a subjective improvement. Three patients underwent VNS and one patient had an initial improvement in vertiginous attacks but experienced persistent severe drop attacks.

Twelve patients revealed a significant (>10 dB) deterioration in their PTA as defined by the AAO-HNS criteria (Figure 1). Five of these patients

TABLE I

DEMOGRAPHIC INFORMATION

Attribute	*n*	Average age* (years)
Male	30	53.3
Female	26	57.2
Respondents	50	54.7
Prior surgery	9	55.9
Total	56	55.1

*Range: 27–87 years

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TABLE II

VERTIGO RESULTS

Patient	Previous surgery	Second procedure	Follow up (months)	Vertigo attacks 6 months before treatment*	Vertigo attacks at end-point of follow up*	Subjective vertigo response following treatment†
1	No	No	3	1–40	0	Complete
2	No	Yes	39	1–40	1–40	Complete
3	No	No	4	1–40	0	Complete
4	No	Yes	36	1–40	0	Complete
5	No	Yes	13	>120	1–40	Complete
6	No	No	6	1–40	1–40	Improved 0
7	No	No	16	1–40	1–40	Complete
8	No	No	17	1–40	1–40	Complete
9	Yes	Yes	36	41–80	1–40	Improved 0
10	Yes	No	31	81–120	1–40	Improved 2
11	No	No	39	41–80	41–80	Improved 0
12	No	No	15	0	0	Dizziness improved
13	Yes	No	2	1–40	1–40	Improved 0
14	No	No	5	>120	1–40	Improved 3
15	No	No	15	1–40	0	Complete
17	No	No	7	1–40	0	Complete
18	No	No	40	1–40	1–40	Same
19	No	No	7	1–40	1–40	Improved 0
20	No	No	7	1–40	1–40	Improved 0
21	No	Yes	28	1–40	0	Complete
22	No	No	6	1–40	0	Complete
23	Yes	No	6	1–40	0	Complete
27	No	No	15	1–40	0	Complete
28	Yes	Yes	36	1–40	0	Complete
29	No	Yes	36	81–120	1–40	Improved 2
30	No	No	34	1–40	0	Complete
31	No	No	34	1–40	1–40	Improved 0
32	No	No	7	41–80	1–40	Improved 1
33	No	No	38	>120	VNS	Improved 3, VNS for drop attacks
34	Yes	Yes	23	81–120	0	Complete
35	No	Yes	22	1–40	1–40	Improved 0
36	No	No	14	1–40	1–40	Improved 0
37	Yes	No	32	1–40	VNS	VNS
39	No	No	7	1–40	1–40	Same
40	No	No	7	1–40	0	Complete
41	No	No	4	1–40	0	Complete
42	No	No	23	0	0	Improved dizziness
44	No	No	35	1–40	0	Improved 1
45	No	No	34	1–40	VNS	VNS
46	No	No	5	1–40	41–80	Worse 1
47	Yes	No	28	1–40	1–40	Same
48	No	No	6	1–40	1–40	Improved 0
49	No	No	15	1–40	0	Complete
50	No	No	18	0	41–80	Worse 2
51	No	No	41	1–40	1–40	Improved 0
52	No	No	34	1–40	1–40	Improved 0
53	No	Yes	33	1–40	0	Complete
55	No	No	2	1–40	1–40	Improved 0
54	No	No	40	1–40	1–40	Improved 0
56	No	No	11	1–40	0	Complete

A second treatment was conducted in nine patients. *The number of vertigo attacks is listed in the categories recommended by the American Association of Otolaryngoloy – Head and Neck Surgery reporting guidelines. †Response was graded as: 'complete' (no vertigo attacks in the last 6 months of follow-up); 'improved' (with the following number indicating the degree of improvement in terms of number of categories – 'improved 0' when the number of attacks was within the same range but with considerable improvement in either the number or severity of attacks), 'same' or 'worse'. VNS = vestibular nerve section during the follow-up period

reported a subjective decline in their hearing, four noticed no change and one thought their hearing had improved (two patients did not respond to the survey). There were no cases of dead ear. The average PTA drop was 18.5 dB (range: 0–28.5 dB). Six patients revealed a significant improvement and 27 showed no change. Due to geographical constraints, 11 patients' pre- or post-operative PTAs, although conducted, were unavailable for analysis. Thirteen out of 50 patients described a subjective decrease in hearing. A significant improvement in the sensation of fullness was reported in 26/46 patients, and 19/48 patients reported a significant improvement in their tinnitus.

Seven patients (of 43) had previously undergone surgery for the treatment of their Ménière's disease. There were no significant differences in the response to gentamicin therapy of this group, in any of the categories.

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Twenty-eight patients underwent their procedures during or after March 2000 and thus were treated with only a single, intra-operative dose of gentamicin. A significant improvement rate in vertigo was found in 23/26 patients, with fullness improving in 12/27 and tinnitus in 10/28. A subjective hearing loss was reported in 5/28 patients. Despite the reduced overall follow up for this group, the results showed an improved response, accompanied by a reduced rate of adverse effects on hearing (Figure 2). Four patients subsequently underwent a second procedure, with no patients in this group requiring VNS at the time of writing.

Long term follow up for all patients was required, with post-operative documentation of PTAs at 18 to 24 months, in order to comply with the reporting standards recommended by the AAO-HNS in 1995.

Discussion

While the use of intra-tympanic gentamicin for the treatment of Ménière's disease is well established, the mode of therapy, dosing regimes and end-point of therapy remain uncertain.[1,2,4,5] The risk of sensorineural hearing loss as a result of gentamicin therapy is obviously a concern, but this also has to be weighed against the natural history of the disease. Many methods of monitoring both the effectiveness and side effects of therapy have been described, many of which require significant time and resources for follow up.[6,6a–9] Much evidence now indicates that ablation of the vestibular response is not necessary to control vertigo.[6,6a,7,10,5] In addition, the likelihood of hearing preservation is thought to be increased with reduced-frequency dosage schedules.[6,6a–8,10,11] This supports the ideal of a single dosing regime. Many centres have described using a titration protocol, an example of which, undertaken at Department of Otolaryngology – Head and Neck Surgery, John Hopkins University, has recently been described by Carey.[12] Injections were repeated every one to three weeks, terminating with evidence of clinical vestibular hypofunction of the treated ear.

Silverstein *et al.*[9] have described an elegant method of directly visualizing the round window with the use of laser-assisted tympanostomy and aural endoscopes, with placement of gelfoam into the round window niche. They reported a 12 per cent rate of complete obstruction and a 17 per cent rate of partial obstruction. This technique, however, is beyond the resources of most otolaryngology departments. Therefore, we propose that the safest and most efficacious mode of delivery is to lift a tympanomeatal flap in order to directly visualize the round window niche, divide adhesions if present, and then place a small piece of gelfoam into the niche. This technique has minimal morbidity and ensures optimal drug delivery. A single dosing regime also negates the need for repeat visits and vestibular and audiological monitoring, at the expense of time and resources.

The most valuable and practicable method of follow up is symptomatic. In our series, a small number of patients required a second procedure, with all but one patient finding initial improvement in symptoms following the first procedure. An important factor in the post-operative course is the presence of disequilibrium (and the duration of this finding). We found no reliable link between the results of post-treatment caloric testing and either the success in controlling vertigo or the likelihood of recurrence. For this reason, we did not routinely repeat vestibular function tests following treatment. Recent literature reviews have reported control or complete ablation of vertigo, ranging from 71–100 per cent of patients.[1,2,5,6,6a,10] In addition, control of fullness was reported in 36–62 per cent of patients and reduction in tinnitus in 42–54 per cent of patients.[1,6,6a,10]

Complete elucidation of the underlying pathophysiology of Ménière's disease remains elusive. Two possible mechanisms of the action of gentamicin are proposed. The recently discovered hormone saccin is thought to arise from the chief cells of the endolymphatic sac; this hormone regulates the function of the striae vascularis.[12] High levels of saccin inhibit the function of the striae, resulting in an increase in the sodium concentration of the endolymph, and thus hydrops. Gentamicin inhibits the synthesis of protein and it is proposed that infusion of gentamicin into the inner ear interferes with the production of saccin, thus reducing the degree of hydrops. Injury to the vestibular dark cells by gentamicin, and subsequent reduction in the production of endolymph, has also been described as a mechanism of action.[13]

Conclusion

There are many proposed methods of delivery of gentamicin in the treatment of Ménière's disease. We propose that a single dose of gentamicin applied directly to the round window provides a significant improvement in symptoms, with acceptable rates of hearing loss. Symptomatic follow up is all that is required; only a small percentage of patients in our series required a second procedure.

- **This study evaluates intra-tympanic gentamicin therapy in 56 patients with Ménière's disease**
- **The authors used a technique involving the elevation of a tympanomeatal flap, followed by direct application of gentamicin to the round window niche**
- **An overall significant improvement in vertigo symptoms was found in 81.3 per cent of cases. There was a 21.4 per cent rate of significant hearing loss**

References

1 Blakley BW. Update on intratympanic gentamicin for Meniere's disease. *Laryngoscope* 2000;**110**:236–40
2 Diamond C. Systematic review of intratympanic gentamicin in Meniere's disease. *J Otolaryngol Otol* 2003;**32**:351–61

https://doi.org/10.1017/S002221510500188X Published online by Cambridge University Press

3 Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium Guidelines for the diagnosis and evaluation of treatment of therapy in Meniere's Disease. *Otolaryngol Head Neck Surg* 1995;**113**:181–5
4 Wanamaker HH. Perfusion of the inner: basic science considerations. *Curr Opin Otolaryngol Head Neck Surg* 2001;**9**:329–32
5 Stockroos R, Kingmz H. Selective vestibular ablation by intratympanic gentamicin in patients with unilateral active Meniere's Disease; a prospective, double blind, placebo controlled, randomized clinical trial. *Acta Oto-Laryngologica* 2004;**124**:172–5
6 Gustafson LM, Pensak ML. Inner ear perfusion therapy: an update. *Curr Opin Otolaryngol Head Neck Surg* 2000;**8**:398–402
6a Eklund S, Pykko I, Aalto H, Ishizaki H, Vasama JP. Effects of intratympanic gentamicin in hearing and tinnitus in Meniere's Disease. *Am J Otol* 1999;**20**:350–6
7 Minor LB. Intratympanic gentamicin for control of vertigo in Meniere's Disease: vestibular signs that specify completion of therapy. *Am J Otol* 1999;**20**:209–19
8 Langman AW. Inner ear perfusion: clinical experience. *Curr Opin Otolaryngol Head Neck Surg* 2001;**9**:333–8
9 Silverstein H, Arruda J, Rosendurg SI, Deems D, Hester T. Direct round window membrane application in the treatment of Meniere's disease. *Otolaryngol Head Neck Surg* 1999;**120**:649–55
10 Pykko I, Ishizaki H, Kaasinen S, Aalto H. Intratympanic gentamicin in bilateral Meniere's disease. *Otolaryngol Head Neck Surg* 1994;**110**:162–7
11 Assimakopoulos D, Patrikakos G. Treatment of Meniere's disease by intratympanic gentamicin application. *J Laryngol Otol* 2003;**117**:10–16
12 Carey J. Intratympanic gentamicin for the treatment of Meniere's Disease and other forms of peripheral vertigo. *Otolaryngol Clin N Am* 2004;**37**:1075–90
13 Qvortrup K, Rostgaard J, Holstein-Rathlou NH, Bretlau P. The endolymphatic sac, a potential endocrine gland? *Acta Otolaryngol* 1999;**119**:194–9

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