The Journal of Laryngology & Otology (2006), ***120***, *730–735*.

doi:10.1017/S0022215106002283
Printed in the United Kingdom
First published online 19 July 2006

Main Article

Intratympanic gentamicin treatment in Meniere's disease: Patients' experiences and outcomes

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Abstract

Objective: The aim of this study was to assess the experiences and outcomes of patients receiving intratympanic gentamicin treatment for Ménière's disease in Norfolk, UK.

Design: This study was based on a retrospective questionnaire survey and a review of patients' medical records.

Setting: Two district hospitals.

Participants: All 29 patients treated between 1999 and 2001, with a minimum follow up of two years post-treatment, were included in the study. Twenty-three patients completed the questionnaires (79 per cent response rate).

Main outcome measures: Glasgow benefit inventory (GBI) and vertigo symptom scale (VSS) scores, plus change in hearing thresholds.

Results: The mean GBI total score was +36, indicating substantial improvement in patients' overall quality of life following gentamicin treatment. The VSS scores demonstrated low levels of vertigo or unsteadiness in treated patients. Three patients suffered deterioration in their hearing thresholds following a single injection of gentamicin. However, 96 per cent of responders stated that they would be willing to have such treatment again, if necessary.

Conclusion: Intratympanic gentamicin treatment ought to be offered to Ménière's patients suffering from disabling vertigo, with the proviso that they be made aware of the possibility of hearing deterioration.

Key words: Ménière's Disease; Gentamicin; Quality of Life; Otologic Surgical Procedures

Introduction

The use of intratympanic gentamicin developed from the recognition that systemic streptomycin was vestibulotoxic. Beck and Schmidt used gentamicin intratympanically and controlled vertigo in 90 per cent of patients; however, 58 per cent experienced hearing loss.[1] The treatment has since evolved, although a variety of gentamicin dosage regimens and methods of administration remain in clinical practice. These include injection through the tympanic membrane, through a grommet, via a Pfleiderer intratympanic catheter and through round window catheters. Several studies have reported vertigo control in about 80 per cent of patients; however, this can be at the expense of hearing loss in up to 25 per cent of cases.[2,3]

The purpose of this study was to assess the experiences and outcomes of Ménière's patients treated with intratympanic gentamicin in Norfolk, UK. We present the results of self-assessed dizziness and quality of life questionnaires. In addition, the effect of treatment on hearing loss (measured by pure tone audiometry), prodromal symptoms and tinnitus was determined and compared with the study findings published in the literature.

Method

Design

The study consisted of a retrospective questionnaire survey and an analysis of patients' medical records.

Patients

Between 1999 and 2001, 29 patients with unilateral Ménière's disease were treated with intratympanic gentamicin in the otolaryngology departments of the James Paget Hospital and the Norfolk and Norwich Hospital, Norfolk, UK.

The diagnosis was based on the history, documented fluctuating sensorineural hearing loss on pure tone audiometry, vestibular tests indicating a relative canal paresis on the affected side and a magnetic

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Accepted for publication: 14 February 2006.

resonance imaging scan excluding an acoustic neuroma. The indication for treatment with intratympanic gentamicin was disabling vertigo (once per day) uncontrolled by medical treatment taken for at least six months. Patients with evidence of middle-ear pathology, allergy to aminoglycosides or disease in the only hearing ear were not offered gentamicin treatment.

Treatment procedure

Written consent was obtained from patients considered suitable for treatment. In the initial cases, a grommet was placed through which gentamicin was injected. The remaining patients received the injection directly through the tympanic membrane 40 minutes after application of Emla cream (a eutectic mixture of lidocaine and prilocaine (Emla) produced by AstraZeneca). Patients were placed supine with their head turned at 30° and 1 ml of 40 mg/ml stock gentamicin was injected. They were then kept in that position for 45 minutes.

Patients were reviewed in the out-patients department a week later and a pure tone audiogram was obtained. Iced water caloric irrigation was performed to identify any residual vestibular function. If nystagmus or dizziness was precipitated by caloric irrigation and pure tone audiometry showed no hearing deterioration, further gentamicin treatment was administered. This was repeated at weekly intervals until no caloric response was obtained. Previous medical interventions, date of injection, symptoms after injection, caloric response and hearing thresholds were recorded.

Participants

All patients with a minimum follow up of two years after gentamicin treatment (based on the American Academy of Otolaryngologists, Head and Neck Surgeons (AAO_HNS) guidelines) were considered eligible for the study. A questionnaire pack with a covering letter and a stamped, addressed envelope was mailed to all eligible patients.

Material

The study pack contained a general questionnaire enquiring about patients' experiences of Ménière's disease and the treatments received.

In addition, the following standard validated questionnaires were enclosed.

*The vertigo symptom scale (*VSS*).*[4] This 35-item, validated, self-reporting questionnaire consists of two subscales: (1) the vertigo scale (20 items), which gives a measure of dizziness severity over the preceding month and is the foremost predictor of dizziness-related handicap; and (2) the autonomic and anxiety scale, which gives an indication of the psychosomatic and sympathetic response to dizziness, thus aiding prediction of the level of dizziness handicap. Symptom frequency is rated on a scale ranging from zero (not at all) to four (several times a day). The vertigo score and the anxiety and autonomic score represent the mean scores of items comprising a particular subscale.

*The Glasgow benefit inventory (*GBI*).*[5] This self-assessment questionnaire is designed to measure changes in quality of life as a result of an intervention. The questionnaire is particularly useful in retrospective studies when information about patients' quality of life before treatment is not available. The scale consists of 18 items, grouped into a 'general' subscale (12 items, e.g. change in feelings of optimism), a 'physical health' subscale (three items, e.g. change in amount of medication) and a 'social support' subscale (three items, e.g. change in level of family support). The answers are based on a five-point Likert scale, ranging from a large deterioration to a large improvement. The various subscale scores and the GBI 'total score' (which takes into account all 18 items) can be calculated using specified formulae. All scores are converted to produce a range of scores on each subscale, from −100 to +100, where −100 represents a large deterioration, +100 indicates a large improvement and zero signifies no change in quality of life.

Analysis

Although the returned packs were anonymous (to reduce bias in patients still being followed up by the consultant), individual patient scores on the various questionnaires were computed and analysed for each returned pack using the Statistical Package for Social Sciences version 11.5 software.

Results

The 29 patients had an age range between 27 and 80 years (mean 54 years). Ten patients were female and 19 male. Twenty-three patients completed the questionnaires (response rate 79 per cent). As the questionnaires were anonymized, the analysis of non-responders could not be performed.

Table I shows the range of medical, surgical and alternative therapy our patients declared they had tried before receiving gentamicin treatment.

Table II shows that, of the patients who returned their questionnaires, most required only one injection of gentamicin; however, one patient required five injections.

Table III shows the degree of discomfort or pain associated with intratympanic gentamicin injection. A significant number of patients experienced moderate to severe pain. Other patients reported little or no

TABLE I

THERAPIES USED BY PATIENTS PRIOR TO INTRATYMPANIC GENTAMICIN

Therapy	Patients (*n*)
Betahistidine	14
Prochlorperazine	14
Cinnarazine	5
Saccus decompression	2
Grommet insertion	1
Low caffeine consumption	1
Acupuncture	1

https://doi.org/10.1017/S0022215106002283 Published online by Cambridge University Press

TABLE II

NUMBER OF INTRATYMPANIC GENTAMICIN INJECTIONS REQUIRED TO CONTROL VERTIGO

Gentamicin injections (*n*)	Patients (*n*)
1	11
2	6
3	5
4	0
5	1

TABLE III

PATIENT COMFORT DURING INTRATYMPANIC GENTAMICIN ADMINISTRATION

Comfort/discomfort level	Patients (*n*)
No discomfort	3
Little discomfort	4
Moderate discomfort	5
Slight pain	1
Moderate pain	6
Severe pain	4

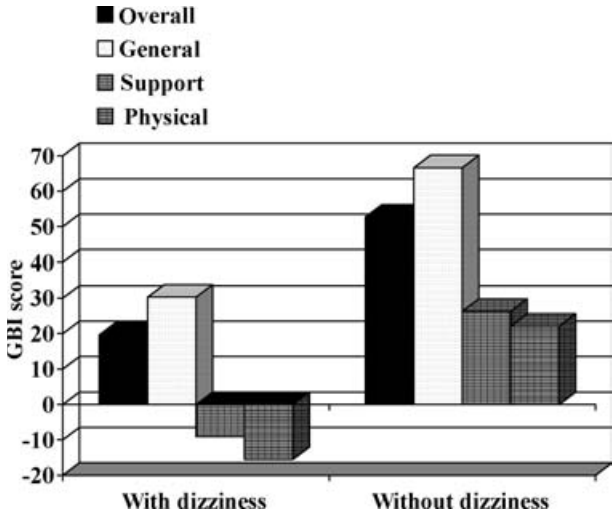

FIG. 1

Glasgow benefit inventory (GBI) scores for patients with and without dizziness after intratympanic gentamicin treatment.

discomfort – this was associated with prior insertion of a grommet under general anaesthetic.

Before gentamicin treatment, the degree of canal paresis ranged from 13 per cent to no response to bi-thermic stimuli, but response to iced water was not tested (median 38 per cent). About three-quarters of patients experienced vestibulotoxic symptoms within a week of gentamicin administration. The presence or absence of vestibulotoxic symptoms did not correlate with the result on subsequent iced water caloric testing.

One patient with documented loss of caloric response after gentamicin injection subsequently developed vertigo. Repeat caloric testing showed some recovery of vestibular function, which required further treatment.

Glasgow benefit inventory scores

The GBI total score for patients receiving gentamicin was +36. Lower scores were achieved within the social support and the physical health subscales.

Figure 1 shows the relationship between the VSS and GBI scores. This could be calculated for each patient since the two questionnaires had been attached to each other in the returned study packs. As expected, the GBI scores were higher in patients experiencing lower levels of unsteadiness and vertigo.

Figure 2 compares the GBI scores of our patients with those of subjects who had undergone various other ENT procedures, including cochlear implantation and tonsillectomy.[5] Quality of life benefit following intratympanic gentamicin therapy compared favourably with treatment outcomes following other ENT procedures.

Table IV compares the level of dizziness in patients who had received gentamicin treatment (i.e. chemical labyrinthectomy) with those who had undergone vestibular nerve section (an example of a surgical ablation, the 'gold standard'). The VSS had been previously administered to patients who had undergone vestibular nerve section as part of acoustic neuroma surgery (translabyrinthine and suboccipital approaches).[6] The VSS scores showed that gentamicin therapy produced a low vertigo score and compared favourably with surgical vestibular ablation.

Pure tone thresholds

From all 29 sets of patient notes, pure tone audiometry at one month post-treatment showed that 33 per cent of patients had experienced a decrease in their hearing of >10 dB (averaged over 500, 1000, 2000 and 4000 Hz). However, half of those patients had

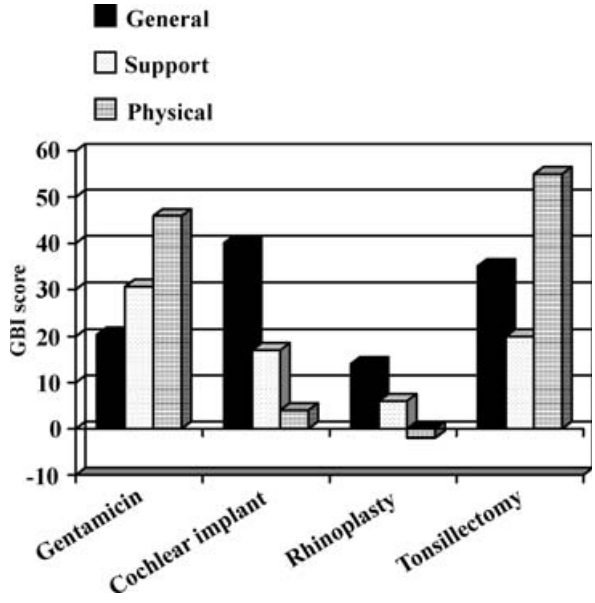

FIG. 2

Glasgow benefit inventory (GBI) scores after intratympanic gentamicin treatment, compared with those for other ENT interventions.

https://doi.org/10.1017/S0022215106002283 Published online by Cambridge University Press

TABLE IV
VERTIGO SYMPTOM SCALE SCORES AFTER INTRATYMPANIC GENTAMICIN TREATMENT AND SURGICAL VESTIBULAR NERVE ABLATION

Treatment	Vertigo score	Anxiety score	Total score
Intratympanic gentamicin			
Mean	0.48	0.55	0.51
Median	0.25	0.37	0.31
Range	0.0–1.6	0.0–2.67	0.0–1.69
Surgical ablation			
Mean	0.32	0.61	0.44
Median	0.20	0.47	0.30
Range	0.0–3.35	0.0–2.8	0.0–2.60

subsequently shown a hearing improvement at various time intervals after treatment. Three patients had developed profound hearing loss or a dead ear after the first gentamicin injection. The hearing thresholds of those patients had ranged from 60 to 90 dB prior to treatment.

Other symptoms

Of the 23 responders, prodromal symptoms had persisted in 70 per cent of patients after gentamicin treatment. Nineteen of the 20 patients with tinnitus before the treatment had continued to experience tinnitus after the treatment.

Patient satisfaction

Despite the persistence of symptoms, 96 per cent of responders were satisfied or very satisfied with their intratympanic gentamicin treatment for Ménière's disease and stated that they would undergo such treatment again, if necessary.

Discussion

Prior to receiving gentamicin therapy, our patients had tried a range of medical and surgical treatments. Until the real benefit of the various management options is rigorously evaluated in prospective, randomized, controlled trials, many would advocate prophylactic low salt diets, diuretics and/or vasodilators.[7–9] In their study, Santos *et al*. reported symptomatic control in 79 per cent of patients with the use of a modified diet and diuretics.[10] However, a Cochrane review found no significant advantage of betahistine over placebo in improving vertigo, hearing loss, tinnitus or aural fullness.[11] A 57 per cent spontaneous resolution rate of dizziness at two years has been reported by Silverstein *et al*.[12]

Surgery is usually advocated after failure of medical treatment. Hearing preservation operations include vestibular neurectomy (which controls vertigo in 94 per cent but carries a 40 per cent risk of hearing loss) and saccus decompression (with a vertigo control rate of approximately 80 per cent and a concomitant lower risk of hearing loss).[13,14] When hearing is poor, a labyrinthectomy is the procedure most commonly performed.

Recent developments have included middle-ear pressure treatment and intratympanic drug therapy. In the former, a grommet is inserted and the Meniett machine used to squeeze excess endolymph out of the inner ear by a direct mechanical effect on the round and oval window membranes.[15] Intratympanic corticosteroids have also been used, but Blakley advised that their use remain investigational until more favourable data is available.[16]

Intratympanic gentamicin has been proposed as an effective treatment alternative. In our series, the majority of patients required only one injection, although 'resilience' was found in one patient, who required five injections. Not all patients experienced post-treatment vertigo – this did not seem to influence the success of an injection (in terms of loss of caloric response).

A significant proportion of patients found gentamicin injection through the tympanic membrane painful, despite Emla cream application prior to treatment. However, 96 per cent of responders were satisfied or very satisfied with their management and would be willing to undergo such treatment again, if necessary.

In our study, patients who experienced lower levels of dizziness achieved higher GBI scores, indicating that symptomatic control of vertigo was associated with improved quality of life. This is somewhat at variance with the results of Soderman *et al*., who found no difference in overall quality of life between patients who had undergone endolymphatic sac surgery or intratympanic gentamicin injections and those who had not been surgically treated,[17] although they reported that their gentamicin-treated patients were less dizzy after the procedure.

Our patients' GBI scores were good overall and compared favourably those for other ENT surgical procedures. This study also showed that patients' VSS scores following intra-tympanic gentamicin were similar to those of patients undergoing surgical ablation of the labyrinth (performed during acoustic neuroma surgery).[6]

- **In this study, 50 per cent of patients with Ménière's disease required only one injection of intratympanic gentamicin, given in the out-patient department**
- **Seventy-five per cent experienced vestibulotoxic effects after injection with intra-tympanic gentamicin, but this did not correlate with the success of treatment**
- **The Glasgow benefit inventory score was +36, a good score for overall quality of life benefit. The vertigo symptom scale showed that gentamicin produced a low vertigo score, comparing favourably with vestibular nerve section**
- **Despite many patients experiencing symptoms after gentamicin therapy, 96 per cent of responders were satisfied with the intervention**

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Thirty-three per cent of our patients developed a hearing loss of >10 dB one month after treatment, half of whom subsequently improved. Three patients had a profound hearing loss or a dead ear after treatment (however, their pre-treatment hearing thresholds were already between 60 and 90 dB). Kaplan *et al*. found hearing loss in 26 per cent of individuals in their study, and when hearing acuity at one month post-treatment remained unchanged it was likely to remain so over the next 23 months.[18] Abou-Halawa and Peo found that 40 mg/ml of stock gentamicin produced similar rates of vertigo control compared with a buffered 30 mg/ml gentamicin solution; however, the higher concentration solution required fewer injections.[19] The risk of hearing loss did not increase with the 40 mg/ml solution provided treatment was stopped at the first indication of vestibular toxicity.

A number of theories have been proposed to explain the observed variability of sensitivity to gentamicin. Walsted suggested that this was due to a decreased patency of communication routes between the inner ear and the cerebrospinal fluid, primarily the cochlear aqueduct.[20] *In vitro* studies have also shown a variation in the round window membrane's permeability to gentamicin.[21] Others have suggested that there is variation in the vestibulocochlear hair cells, perhaps due to genetic variability.[22] Identification of the gene(s) responsible could lead to pre-treatment testing to identify those patients requiring a reduced dose of gentamicin. Further studies are required to determine the mechanism causing the heightened sensitivity observed in some individuals, to enable prediction of which patients require a reduced gentamicin dosage.

Prodromal symptoms persisted in 70 per cent of our patients. This would suggest that hydrops remained and that gentamicin's principal effect was on the vestibular hair cells and not the dark cells. Our survey confirmed Yetiser and Kertmen's finding that gentamicin had no effect on tinnitus.[23]

The reason why gentamicin can have a reversible effect (seen in one of our patients) remains unclear. Kaasinen *et al*. followed up patients for two years after initial treatment; 44 of their 93 patients required further injections.[24] The use of the iced water caloric test to assess vestibular function may be a less sensitive test of vestibular ablation. De Waele *et al*. found that a third of their 22 patients had recovered vestibular responses within two years, after initial loss of caloric responses.[25] However, another study showed that no patient developed vertigo once galvanic responses had been abolished by gentamicin treatment.[19]

In view of the risk of profound deafness resulting from gentamicin treatment, it may be prudent to keep the gentamicin dosage at its current level, rather than increasing the dosage or the number of injections until no galvanic response is obtained. Should symptoms and vestibular responses on the treated side recur, the possibility of further gentamicin treatment can be discussed with the patient.

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Miss W Smith takes responsibility for the integrity of the content of the paper.
Competing interests: None declared