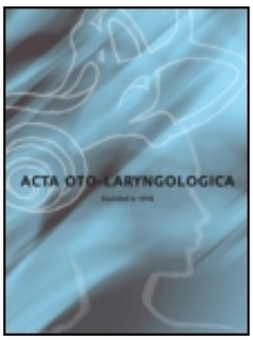

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Selective Vestibular Ablation by Intratympanic Gentamicin in Patients with Unilateral Active Ménière's Disease: A Prospective, Double-blind, Placebo-controlled, Randomized Clinical Trial

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Objective—To establish the efficacy of intratympanic gentamicin treatment in patients with unilateral Ménière's disease.
Material and Methods—This was a prospective, double-blind, randomized clinical trial of intratympanic gentamicin versus intratympanic buffer solution (placebo) in patients with established active Ménière's disease in the affected ear. Outcome measures included the number of vertiginous spells, degree of sensorineural hearing loss, labyrinthine function and labyrinthine asymmetry.
Results—Topical gentamicin provided a significant reduction in the number of vertiginous spells, although a "placebo effect" was also observed. Sensorineural hearing loss did not occur in the gentamicin group, although some deterioration occurred in the placebo group.
Conclusions—Intratympanic gentamicin is a safe and efficient treatment for the vertiginous spells associated with Ménière's disease. When applied early in the course of the disease, it may prevent some of the sensorineural hearing deterioration associated with it. *Key words: aminoglycosides, gentamicin, intratympanic, Ménière's disease, sensorineural hearing loss, vertigo treatment*.

INTRODUCTION

Patients with active unilateral Ménière's disease (MD) suffer from unpredictable vertiginous attacks, often accompanied by nausea and vomiting, together with fluctuating sensorineural hearing loss (SNHL), tinnitus and a sensation of pressure in the affected ear. In spite of increasing insight into the pathogenesis of MD, therapeutic efforts have limited success in these patients. Surgical ablation of the affected labyrinth aims to prevent vertiginous spells, albeit at the cost of deafness, and vestibular neurectomy involves an intracranial intervention, with its associated morbidity. The use of topical aminoglycosides is a less invasive method of ablation of the affected vestibular end organ and one in which cochlear function is preserved.

Fowler (1) observed that systemic administration of ototoxic antibiotics leads to loss of both cochlear and vestibular function. Parenteral use of ototoxic antibiotics causes damage to both vestibular organs and therefore leads to a lack of balance and spatial orientation. To prevent this, Schuknecht (2) introduced intratympanic application of the aminoglycoside streptomycin to the affected ear, aiming to chemically ablate the vestibular apparatus and thus reduce the number of vertiginous spells. The aminoglycoside antibiotic gentamicin sulfate is supposed to affect the vestibular apparatus more and the hearing organ less, and thus has a dose-dependent "vestibular affinity" (3). Intratympanic gentamicin was used by various authors (4, 5) to achieve selective vestibular ablation in patients with active MD. Prospective evaluation of this treatment modality revealed a reduction in vertiginous spells in approx. 90% of patients (6, 7). Sensorineural deafness occurs in about 10% of patients, SNHL in about 15% and sensorineural hearing improvement in about 60% after gentamicin treatment. The adverse events of gentamicin vary with the dose used and the time interval between repeated intratympanic applications (8–11). Over time, MD leads to SNHL, whilst vertiginous attacks may subside. Therefore, in this study, the therapeutic value of intratympanic gentamicin in MD is evaluated against placebo in a prospective, randomized, double-blind clinical trial.

MATERIAL AND METHODS

The study was conducted in a tertiary referral neuro-otologic centre. Diagnosis of MD was made according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) criteria for definite MD. A diagnostic protocol was used with the aim of excluding an underlying etiology of the symptoms (12). Treatment of patients was done in four increasingly invasive steps, as follows: (i) supportive therapy; (ii) systemic oral medication; (iii) selective chemical labyrinthine ablation; and (iv) selective vestibular neurectomy.

The study was conducted based on the hypothesis that intratympanic application of gentamicin in patients with MD causes a significant reduction in the

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number of vertiginous spells with minimal side-effects and risks.

A double-blind, prospective, placebo-controlled, randomized clinical trial was performed in 22 patients with a follow-up of at least 6 months. Power analysis showed that 16–22 patients were required if it was assumed that a reduction in the number of vertiginous spells of 50% was a statistically significant therapeutic effect.

The hospital medical ethics committee approved the study protocol and, before inclusion in the trial, all patients signed an informed consent form complying with European Good Clinical Practice regulations.

In 10 patients with a diagnosis of MD who fulfilled the inclusion criteria but not the exclusion criteria (Table I) a paracentesis was done in the affected ear, followed by intratympanic application of either the aminoglycoside antibiotic gentamicin (30 mg/ml in a buffer solution, pH 6.4) (gentamicin group) or buffer solution only (control group). The application protocol was standardized as shown in Table II. Either gentamicin or placebo was left in the middle ear. Randomization was performed by the hospital pharmacist, who was the only person who knew whether placebo or gentamicin was given before the end of the study period. Applications were repeated every 6 weeks until either control of symptoms was achieved or one of the exclusion criteria was met. Prior to each application, the number of vertiginous spells and subjective hearing changes were noted, pure-tone and speech audiometry were performed and quantitative measurements of labyrinthine function were made.

Statistical analysis was done using *t*-tests and Mann–Whitney tests where applicable.

RESULTS

Between October 2000 and October 2002, 22 patients (9 females, 13 males) were included in the study. Twelve patients received gentamicin and 10 received placebo. Mean age at treatment was 59 years (range 34–74 years) in the gentamicin group and 58 years (range 45–70 years) in the placebo group, this difference not being statistically significant ($p = 0.41$). The left ear was involved in 14 cases and the right in 8. The follow-up period varied between 6 and 28 months.

The number of applications performed was 1.5 ± 0.51 (mean $\pm$ SD) in the gentamicin group and 2.8 ± 2.7 in the placebo group ($p = 0.11$).

Table I. *Inclusion and exclusion criteria*

Inclusion criteria
Active MD (according to AAO–HNS criteria)
Known underlying cause excluded using a diagnostic protocol
Conservative/medical treatment for at least 6 months has proven unsuccessful
Incapacitating vertigo attacks occurring at least monthly and recorded for at least 6 months
Unilateral pathology
Informed consent obtained
Exclusion criteria
Cumulative gentamicin dose ≥ 360 mg for 12 applications
Cumulative treatment time after first treatment > 6 months
Perceptive hearing loss after treatment ≥ 15 dB for 2 subsequent octave steps in the pure-tone audiogram
Contralateral (neuro)otological pathology
Ipsilateral middle ear pathology
Allergy to aminoglycosides

Table II. *Application protocol*

Gentamicin (4 ml; 30 mg/ml) in a buffered solution (pH 6.4) or placebo is prepared in a 4-ml syringe and warmed in the physician's breast pocket
The patient is in the supine position with the affected ear facing upwards
Local anaesthesia of the tympanic membrane is achieved by application of a cottonoid soaked in 10% lidocaine spray against the tympanic membrane
A spinal puncture needle (15-cm long) is connected to the syringe and bent to an angle of $\pm 30^\circ$
After aspirating any remaining lidocaine, a paracentesis is performed just anterior to the umbo
The needle tip is introduced slightly into the middle ear cavity
The hypo- and mesotympanum are filled with either gentamicin or placebo until the fluid meniscus is touching the paracentesis opening and fluid flows back into the external meatus
The patient remains in this position for 45 min
Gentamicin or placebo is left in the middle ear

In the gentamicin group, the number of vertiginous attacks per year was 74 ± 114 (AAO–HNS Class B–C) before treatment and 0 after treatment (AAO–HNS Class A) ($p = 0.002$), compared to 25 ± 31 (AAO–HNS Class B–C) before treatment and 11 ± 10 (AAO–HNS Class B) after treatment ($p = 0.028$) in the placebo group.

In the gentamicin group, all 12 patients reported no complaints of vertiginous attacks 6 weeks after the last treatment and during follow-up. In the placebo group, one patient reported a significant reduction in the frequency of vertiginous attacks, five reported some reduction and four reported no benefit at all.

In the gentamicin group, the cumulative caloric response in the treated ear was $16 \pm 13.4^\circ$/s before treatment and $9.4 \pm 12.8^\circ$/s after treatment ($p = 0.091$). In the placebo group, the cumulative caloric response in the affected ear was $19 \pm 13.1^\circ$/s before treatment and $14 \pm 8.3^\circ$/s after treatment ($p = 0.153$).

Vestibular asymmetry in the gentamicin group was $54\% \pm 19\%$ before and $68\% \pm 33.6\%$ after treatment ($p = 0.182$). Vestibular asymmetry in the placebo group was $46\% \pm 17.1\%$ before and $55\% \pm 24\%$ after treatment ($p = 0.130$).

Hearing was reported unchanged by all patients, i.e. no deafness or significant hearing loss occurred. The extended Fletcher index at 500, 1000, 2000 and 4000 Hz in the gentamicin group was 60 ± 18.7 dB HL (AAO–HNS stage 3–4) before treatment and 54 ± 20 dB HL (AAO–HNS stage 3–4) after treatment ($p = 0.17$). In the placebo group, the extended Fletcher index was 53 ± 16.5 dB HL (AAO–HNS stage 3–4) before and 58.8 ± 20 dB HL (AAO–HNS stage 3–4) after treatment ($p = 0.24$).

DISCUSSION

This study confirms the hypothesis that intratympanic application of gentamicin in patients with MD causes a significant reduction in the number of vertiginous spells: in fact, it makes the attacks disappear. Placebo is never able to achieve this, although a placebo effect is present in topical gentamicin treatment: half of our placebo-treated patients experienced some reduction in vestibular complaints.

It is remarkable that total lateral canal caloric areflexia is not necessary in order to make the vertiginous attacks disappear, as in some of our asymptomatic patients some vestibulo-ocular reflexes could still be elicited from the affected ear after gentamicin treatment using caloric stimulation of the lateral semicircular canal. The value of caloric stimulation of the lateral canal as a method of determining therapeutic effect is questionable, as it is difficult for the gentamicin to affect, for example, posterior canal function. The other canals and the statolith organs are not routinely tested and may remain functional even in a patient in whom the lateral canal has been ablated. In one of the patients reported we encountered a recurrence of vertiginous attacks 1–2 years after successful gentamicin vestibular ablation. In our experience, this occurs rarely either in patients with total labyrinthine ablation or in those with some remaining caloric function. There may be regeneration of hair cell function in these patients, as was demonstrated in animal experiments (13). These patients usually respond well to another gentamicin application. Therefore, gentamicin vestibular ablation should be directed by the complaints of the patient and not by labyrinthine function measurements. This also reduces the risk of causing unnecessary SNHL.

Deterioration of sensorineural hearing as a result of its ototoxic action is one of the prime concerns with topical gentamicin treatment. Clinical and experimental evidence indicates that this risk can be reduced by using a low dosage and a long time interval between repeated injections (14). This was confirmed in our study: we found that sensorineural hearing was not altered significantly in gentamicin-treated patients. Hearing had a tendency to deteriorate in the placebo-treated patients, due to the natural course of the disease, although this finding was not significant. This suggests that early treatment with topical gentamicin may preserve remaining sensorineural hearing in active MD. This should be weighed against the risk of sensorineural hearing being damaged as a result of the ototoxicity of gentamicin, which in our patients was comparably much smaller. In most cases this decision merely represents a dilemma for the doctor: most patients do not care very much about the hearing level in the affected ear, as it is already much worse compared to that in the healthy ear. However, a case can be made for gentamicin ablation to be used earlier. This is currently a subject of further investigation.

Gentamicin treatment has its drawbacks. Although all of our gentamicin-treated patients were quite satisfied with the disappearance of unpredictable vertiginous attacks, problems compatible with unilateral vestibular hypofunction were revealed after treatment: orientation skills whilst making rapid head movements in the direction of the affected labyrinth were impaired at first and posture and gait control were limited. These problems may be influenced positively by vestibular adaptation exercises, although they resolved spontaneously in all our patients.

CONCLUSIONS

Intratympanic gentamicin is a safe and efficient treatment for vertiginous attacks occurring as a

symptom of MD. The risk of sensorineural hearing deterioration commonly attributed to this treatment is limited as long as a low dosage and a long dosage interval are used, and is probably smaller than the deterioration in sensorineural hearing that occurs as a consequence of the natural course of the disease. We recommend that this treatment should be guided by the vertiginous complaints of the patients and not by the level of caloric responsiveness of the lateral canal of the affected labyrinth. In our experience, a vestibular rehabilitation training programme is not a prerequisite for a favourable outcome of this treatment.

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