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Intentional Ablation of Vestibular Function Using Commercially Available Topical Gentamicin-Betamethasone Eardrops in Patients With Meniere's Disease: Further Evidence for Topical Eardrop Ototoxicity

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Objective: **To determine whether the controversial findings of suspected ototoxicity from commercially available gentamicin sulfate and betamethasone sodium phosphate eardrops can be used in a therapeutic fashion to ablate (or attenuate) vestibular function in patients with unilateral Meniere's disease.** ***Study Design:*** **Prospective case review.** ***Methods:*** **At a tertiary care dizziness unit at the University Health Network, Toronto General Hospital, University of Toronto (Toronto, Ontario, Canada), adults with unilateral Meniere's disease undergoing intratympanic ablation therapy were studied. After insertion of a tympanostomy tube with the patient under local anesthesia, patients instilled gentamicin containing eardrops three times daily until they became vertiginous for longer than 24 hours and then for an additional 2 days longer or for 1 month, whichever came first. Electronystagmographic caloric test responses were measured before treatment using bithermal water caloric and after treatment using air caloric tests. Main outcome measures included clinical titration of drops to the onset of prolonged vertigo. As well, post-treatment findings on electronystagmography and audiometry were compared with pretreatment testing.** ***Results:*** **Twenty patients were available for review. Fifteen patients had a significant reduction in caloric test responses compared with pretreatment values; among them, 10 patients had absent air caloric test responses on the treated side. In 10 patients hearing worsened according to the 1995 American Academy of Otolaryngology—Head and Neck Surgery Committee on Hearing and Equilibrium Guidelines for reporting in Meniere's disease.** ***Conclusions:*** **Topical gentamicin-betamethasone eardrops can pass through a tube into the middle ear, where they may prove primarily vestibulo-ototoxic patients with Meniere's disease. The study further confirms clinical observations that gentamicin-containing eardrops might prove ototoxic, especially in noninflamed ears with a tympanic membrane defect.** ***Key Words:*** **Gentamicin ablation, intratympanic gentamicin, topical gentamicin, Meniere's disease, ototoxicity.**

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INTRODUCTION

Eardrops containing gentamicin or other related aminoglycosides are commonly prescribed by primary care physicians and otolaryngologists for treatment of external otitis, chronic suppurative otitis media, and discharging tympanostomy tubes. Although topical aminoglycoside ototoxicity appears to be infrequent, there has been a genuine concern that this might develop if eardrops were to reach the middle ear in the presence of a tympanic membrane (TM) perforation or defect.[1] Until recently, attention had been primarily focused on possible cochlear ototoxicity, based on a small number of largely anecdotal case reports describing patients with sensorineural hearing loss following application of eardrops.[2] For this reason, cautionary warnings have been provided for most ototopical agents, advising against their use in the presence of a TM perforation. Despite this concern, as of 1992, most otolaryngologists in the United States felt comfortable

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prescribing aminoglycoside-containing drops for a draining perforation or for infective tympanostomy tubes.[3]

The development of vestibular ototoxicity associated with systemic gentamicin administration has been a well-recognized phenomenon since its introduction in the 1960s. Paradoxically, this property of gentamicin has been used therapeutically since the late 1970s for the topical ablation of vestibular function in the treatment of unilateral Meniere's disease. Different treatment protocols in Meniere's disease have been introduced subsequently, with vertigo control rates generally in the order of 80% to 100%.[4–16]

The suspicion that the prolonged clinical use of commercially available gentamicin-containing eardrops might result in inadvertent vestibular ototoxicity has been documented recently. In 1999, Bath et al.[17] updated a study of 16 patients with suspected topical ototoxicity from Garasone eardrops (1 mL contains 3 mg gentamicin sulfate and 1 mg betamethasone sodium phosphate (Schering, Canada Inc., Pointe-Claire, Quebec, Canada). Patients either had perforated tympanic membranes or tympanostomy tubes in place. All had applied the drops for more than 7 days before developing a vestibular loss. The study also reported on one patient with unilateral Meniere's disease who underwent deliberate vestibular ablation with the same commercially available drops. The patient had normal pretreatment electronystagmographic (ENG) caloric test responses and achieved an absent response with air caloric tests after treatment.

As a result of these findings, we were encouraged to further investigate the ototoxic potential of a common, commercially available gentamicin-containing ototopical preparation in a select group of patients with incapacitating unilateral Meniere's disease. The objectives of the present study were threefold: 1) to determine whether commercially available gentamicin containing eardrops could access the middle ear through a conventional tympanostomy tube, 2) to determine whether these drops could result in either vestibular or cochlear ototoxicity, and 3) to serve as a foundation for future studies to assess the potential therapeutic role of commercially available gentamicin-containing eardrops for patients with incapacitating Meniere's disease.

PATIENTS AND METHODS

All patients were seen in the Department of Otolaryngology, University Health Network, University of Toronto (Toronto, Ontario, Canada) by the senior authors (J.A.R. and M.L.B.). All had definite unilateral Meniere's disease as defined by the 1995 American Academy of Otolaryngology—Head and Neck Surgery Committee on Hearing and Equilibrium (AAO-HNS CHE) Guidelines for the Diagnosis and Evaluation of Therapy in Meniere's Disease.[18] Most patients initially received medical therapy that could have included dietary salt restriction, diuretics, and betahistine dihydrochloride (Serc, Solvay Pharma, Scarborough, Ontario, Canada) for a minimum of 6 months and had achieved limited or no control of their vertiginous attacks. Treatment with topical intratympanic, commercially available gentamicin-betamethasone eardrops was initiated between April 1999 and November 2000.

Audiovestibular Testing

A pretreatment audiogram and electronystagmogram with bithermal water caloric testing was obtained before the intended procedure. These two tests were repeated, typically, 1 to 4 months after treatment. Audiometry included pure-tone testing, speech reception thresholds, and speech discrimination scores. The pure-tone average (PTA) was calculated using frequencies of 0.5, 1.0, 2.0, and 3.0 kHz. Change in hearing was defined by the 1995 AAO-HNS CHE criteria, which considered a change of 10 dB or more or a change in word recognition score (speech discrimination) of 15% or more to be clinically significant.[18]

Pretreatment bithermal ENG caloric test responses were performed, and the excitability difference (ED) between the affected and nonaffected sides calculated. Post-treatment caloric test responses were measured using ENG air caloric tests (ears were stimulated alternately with air at 5°C for 30 seconds) (model NCA-105, ICS Caloric, Addison, IL), because of the tympanostomy tube,[18] and the ED was calculated.[19] In our center, an ED of 0% to 15% was considered within normal limits, and an ED of 16% to 25% was considered a mild, 26% to 50% a moderate, 51% to 90% a severe, and greater than 90% a profound caloric reduction.[20] No response after treatment implied no discernible response to air caloric testing above any spontaneous nystagmus in the caloric test position.[20] A vestibular ototoxic effect was considered when there was a deterioration in one or more ED groupings.

Treatment Protocol

A tympanostomy tube (Sheppard Grommet Vent Tube, 1.14-mm internal diameter, Smith & Nephew Inc., Bartlett, TN) was inserted into the posteroinferior quadrant of the TM under topical anesthesia (phenol or eutotic mixture of local anesthetics [EMLA], Astra Pharma Inc., Mississaugua, Ontario, Canada). Topical gentamicin-betamethasone eardrops were prescribed, and patients were instructed to instill three or four drops (approximately 0.1–0.15 mL) three times daily, followed by alternating tragal pressure against the ear canal to "pump" the drops while lying with the affected ear upright for 15 minutes. The patients were instructed to continue until prolonged vertigo or imbalance occurred for longer than 24 hours and then to continue drop instillation for another 2 days or for a maximum of 1 month, whichever came first.

RESULTS

Between April 1999 and November 2000, 23 patients in total were treated with intratympanic commercially available gentamicin-betamethasone ototopical drops. Three patients were not available for post-treatment follow-up. However, these three patients were asymptomatic for further vertigo when contacted by means of a telephone interview 2 to 8 months after treatment.

Twenty patients in total were available for review (11 men and 9 women). Mean age was 50.1 years. The right ear was affected in 9 patients, and the left in 11. Patients had symptoms of Meniere's disease for a duration of 1 to 13 years. Three patients included in the present study had previously undergone intratympanic gentamicin therapy that had failed to control their vertigo and were included to further assess the effects in the present study on audiovestibular function. Two of the three patients (patients 11 and 18) had received treatment in the same ear using a fixed-treatment protocol with concentrated intratympanic gentamicin (24 mg gentamicin/mL injected 11/2 cc three times daily for 4 days) 4 to 6 years previously. The third patient (patient 17) had undergone the same treat-

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ment with these same drops 6 months earlier without success. This patient did not initially develop symptoms suggestive of ototoxicity after 3 weeks and subsequently discontinued treatment. She continued to demonstrate a mild vestibular loss on post-treatment ENG air caloric testing with no change in ED groupings or her hearing. No patient in the present study had previously undergone other surgery for Meniere's disease.

The majority of patients developed symptoms in the first 2 weeks after starting treatment. Duration of treatment was 9 to 28 days (mean duration, 15 days). Patients recalled their symptoms as being compatible with vertigo, imbalance, lightheadedness, or nausea, or a combination of these. Post-treatment clinical assessments, as well, sought signs (not listed) that specified completion of therapy.[10]

Table I lists the patients and the observed ototoxic effects following the instillation of commercially available gentamicin-betamethasone eardrops.

Vestibulotoxicity

Table I and Figure 1 list and demonstrate, respectively, the comparative caloric ENG results before and after treatment. Before treatment, six patients had an ED greater than 50% and no patient had an absent caloric response. After treatment, 5 patients had an ED greater than 50% and 10 had absent caloric responses. In total, 15 patients realized a significant decrease in ENG caloric test responses on the affected side, as reflected by increasing excitability differences or an absent response after treatment. Three patients demonstrated no or minimal change in ED, and in two patients (patients 6 and 12) there was an apparent improvement.

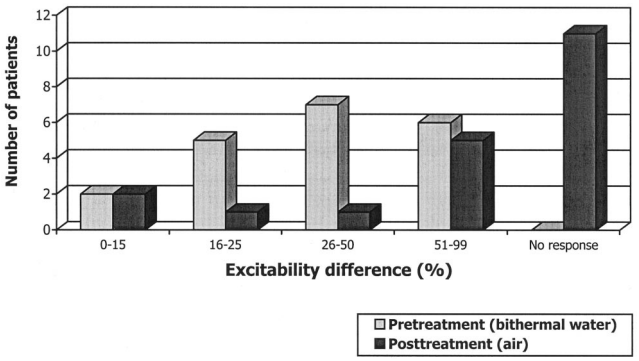

Fig. 1. Caloric test responses before and after treatment in 20 patients with Meniere's disease who were treated with a Garasone ablation protocol through a tympanostomy tube.

Cochlear Ototoxicity

Pretreatment hearing acuity was variable, ranging from normal to no measurable hearing. Ten patients had

TABLE I.
Patients' Pre- and Posttreatment Audiometry and ENG Caloric Test Results.

		Pretreatment			Posttreatment			
Patient No.	Age/Sex	ENG Calorics* ED (%)	PTA	SDS%	ENG Calorics* ED (%)	PTA	SDS%	Ototoxic Effects
1	63/F	30	53	CNT	Absent‡	55	16	Vest. loss
2	75/M	68	100	CNT	Absent	100	CNT	Vest. loss
3	51/F	0	40	72	90	22	92	Vest. loss & hearing improvement
4	38/F	35	80	12	Absent	100	14	Vest. & hearing loss
5	30/M	45	15	100	86	30	100	Vest. & hearing loss
6	56/M	51	13	96	4	15	96	Improved vest. function
7	39/M	22	60	40	Absent	100	CNT	Vest. & hearing loss
8	47/F	19	15	88	Absent	13	96	Vest. loss
9	61/M	29	40	72	Absent	30	92	Vest. loss
10	44/M	36	67	CNT	Absent	22	88	Vest. loss & hearing improvement
11	62/M	75	57	32	52	55	64	Hearing im provement
12	30/F	64	60	CNT	5	80	CNT	Improved vest. function & hearing loss
13	58/M	75	75	CNT	Absent	95	CNT	Vest. & hearing loss
14	49/F	20	50	36	66	68	16	Vest. & hearing loss
15	71/M	28	70	8	40	53	32	Hearing improved
16	54/M	18	53	12	72	70	0	Vest. & hearing loss
17	22/F	22	80	32	18	78	12	Hearing loss
18	34/M	44	38	72	Absent	55	80	Vest. & hearing loss
19	69/F	80	40	72	Absent	45	25	Vest. & hearing loss
20	72/F	9	50	10	9	50	0	Vest. Loss

*Pretreatment ENG calorics were performed with alternate bithermal water irrigation.
†Posttreatment ENG calorics were performed with air caloric method.
‡An ED of 100%. CNT-could not be tested; Vest = vestibular.
ENG = electronystagmography; ED = excitibility difference; PTA = pure tone average (0.5, 1.0, 2.0, 3.0 KHz); SDS% = speech discriminations score.

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worsening of hearing (in patient 5, this occurred mainly in the high-frequency range greater than 4 kHz). In four patients (patients 3, 10, 11, and 15) hearing improved, whereas in the remaining six patients no change was noted. In the small subset of three patients who had been previously treated with topical gentamicin, the PTA worsened in one patient (patient 18) and speech discrimination worsened in another patient (patient 17) and improved in one patient (patient 11). Average follow-up was 7 months. Except for ototoxicity no other complications were encountered.

DISCUSSION

Following preliminary reports from Beck and Schmidt[4] and Schmidt and Beck,[5] numerous authors have reported on the therapeutic use of intratympanic gentamicin in the treatment of unilateral Meniere's disease.[6–16] As shown in Table II, treatment protocols have varied with respect to frequency, concentration of gentamicin (6–40 mg/mL), total dosage and duration (i.e., 1–12 doses of 6–40 mg gentamicin delivered three times daily to once every 2 weeks), type of delivery system used (e.g., transtympanic injections, injections through a tympanostomy tube or ventilation tube, catheter injections), and how the end point of therapy was determined (fixed vs. titration protocol).

It should be clearly stated that our study was not intended to report results of this protocol for symptom control in Meniere's disease. According to the 1995 AAO-HNS CHE Guidelines for the Diagnosis and Evaluation of Therapy in Meniere's Disease,[18] results of treatment for Meniere's disease should be reported under the vertigo control rate, functional level, and hearing status, the most important aspect of reporting being the requirement of a minimum 2-year follow-up. Nevertheless, our goal in the present study was to primarily demonstrate in a prospective fashion that commercially available gentamicin-betamethasone–containing eardrops can prove ototoxic if used in a prolonged fashion when a tympanostomy tube is present.

In the past, reports of suspected ototopical gentamicin ototoxicity have been largely criticized for being anecdotal and retrospective. Because pretreatment caloric function was largely unknown, there was legitimate concern about whether the suspected changes in vestibular function actually arose from the use of these drops. Having performed both pretreatment and post-treatment audiometric and caloric testing in the present study, we think we have overcome some of these criticisms.

In the present study we evaluated whether a commonly prescribed commercially available ototopical preparation containing gentamicin and betamethasone could penetrate the middle ear through a tympanostomy tube, be absorbed into the inner ear, and subsequently result in ototoxicity if used in a prolonged clinical fashion. Findings supportive for an ototoxic event related to this intervention included a clinical history of prolonged vertigo lasting days during treatment, post-treatment signs of vestibular deafferentation (e.g., the presence of nystagmus after head shake or a positive result on head-thrust or Halmagyi maneuver),[10] and changes in the pretreatment and post-treatment audiometry and ENG caloric testing.

TABLE II.
Summary of Pre- and Posttreatment Using ENG Caloric Responses in Studies on Intratympanic Gentamicin Therapy in Unilateral Meniere's Disease.

Study	No. of Patients	Protocol	Method of Application	Dose per Treatment	Frequency of Treatment Sp.	No. of Treatments	Pretreatment Caloric Responses	Posttreatment ENG-Caloric Responses
Youssef & Poe [6*]	37	T	II	30 mg?	Weekly	1–8	Not recorded	Timing-? 23% had decreased responses- 0–4°/sec
Kaaslinen et al [7*]	93	T	II	12–20 mg	Daily	1–4	Not recorded	Timing-? Absent IW-39% Positive IW only - 25%
McFeely et al [8*]	22	F	TT with catheter or polyethylene tube	26.7 mg	3 day (4 days)	12	Average ED 48%	Timing-? Average ED 92% Absent IW −75%
Minor [9*]	34	T	II	8–16 mg	Weekly	1–6	Canal paresis (ED >20- 56%	At 3 months: Canal paresis 90%. Absent IW -22% Positive IW only- 25%
Silverstein et al [10*†]	32	T	Injected into middle ear gelfoam	5–8 mg	Every five days to monthly	(1 to ?)	Average ED.30–49% (3 protocols)	At 1 month: Average ED- 59–76%. Absent bithermal 2% Absent IW -25%
Atlas & Parnes [11*] (1999)	68	T	II	13–26 mg	weekly	1–8	Mean bithermal response-24°/s	At 3 months: Mean bithermal response-7°/s Positive IW only- 16% Absent I W -45%
Kaplan et al[12*]	90	F	TT with catheter	19 mg	3 times a day	12	Caloric weakness- 82% IW+ only 8% Absent IW- 1%	2 years IW+ only 16% Absent IW- 72%
Murofushi et al[13]	19	T	II	15–30% X 1–5	Daily		Mean bithermal response 15°/s)	Timing- 1–2 months. Mean bithermal response
Harner et al[14]	43	T	II	30 mg X 1–4	Monthly		ED >20%- 72%	ED> 20%- 94%

*Studies reporting according to AAO-HNS CHE guidelines (1985/1995)
†Gentamicin solution was applied to gelfoam placed against the round membrane.
T = titration; F = fixed, II = intratympanic injection; TT = tympanostomy tube; ED = excitability difference; IW = ice water caloric response.

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Regarding laboratory testing, it is well recognized that the ENG caloric test is somewhat limited in its ability to completely assess vestibular end organ function (i.e., theoretically, it only records function of the horizontal semicircular canal and even this is usually thought to reflect its lower frequency range). Nevertheless, its chief value resides in the localization of a diseased side and its ability to provide a quantitative measure of vestibular end-organ function for comparison. For this reason, it still remains the gold standard for the assessment of vestibular function.

With regard to laboratory testing, our methodology for testing vestibular end-organ function in the present study was somewhat inconsistent because it was based on a comparison of pretreatment bithermal ENG (water) caloric testing and post-treatment air caloric tests (because a tympanostomy tube was still in place). We acknowledge that ENG air caloric tests may not be as quantitatively precise as bithermal ENG water caloric tests; nevertheless, we think it is the relative comparison between sides that still remains the most important aspect for consideration.[19] In general terms, the thermal stimulus from an air caloric test reaching the middle ear directly through a tympanostomy tube would be expected to result in a greater or an artifactually *increased* caloric test response, not the decreased response that was usually seen after treatment. With this in mind, it is quite probable that any attenuation or ablation in air caloric activity on the treated side was actually even more pronounced taking into account this phenomenon. Conversely, it is possible that the presence of a tympanostomy tube may, in certain circumstances, have biased the caloric test response in favor of what appeared to be no effect (i.e., false-negative result) from treatment in a few patients. This may explain the results of the two patients who had an *apparent improvement* in post-treatment air caloric ED.

In the future, we think improvements in methodology would certainly strengthen our position that prolonged use of ototopical gentamicin-containing eardrops are primarily vestibulo-ototoxic. Improvements could include the use of a closed-loop irrigation system for caloric testing or insertion of a pliable tympanostomy tube that could be easily withdrawn immediately after treatment. Then, rapid healing of the TM would allow for formal ENG caloric testing to occur a short time later.

Overall, 75% of treated patients in the present study had evidence of ED change on ENG air caloric testing which was highly suggestive that a vestibulo-ototoxic event had occurred. Although we are relatively certain our intervention caused this, another consideration would be whether the decrement in caloric activity seen in the majority of patients after eardrop use was part of the natural history or a result of fluctuation of vestibular function seen in Meniere's disease. There is no absolute way to refute this, beyond the statistical unlikelihood that a pronounced change in vestibular function would occur in this many patients within a 1- to 4-month time span, with few showing random improvements in function. In the absence of a known comparator (either from randomization of patients or from historical controls) and with there being valid concerns regarding our methodology, any conventional statistical analysis cannot be performed. Nevertheless, the finding of even one patient in the present study with worsening of caloric activity (or cochlear thresholds) in the treated ear might be significant if one takes into consideration the previous estimate for topical ototoxicity by Roland[2] of 1 in 10,000. However, in the absence of a comparator, which could be provided through randomization, standard statistical tests such as the Fisher Exact test or the Student t test for paired or unpaired data cannot be used. Nevertheless, if established 95% nominal confidence intervals are applied to the data, the statistical likelihood that the effect witnessed occurred as a result of the intervention ranges from 0.56 to 0.94. In other words, the effect of this protocol being responsible for a change in ED on caloric testing ranges from an incidence slightly greater than the toss of a coin to an almost assured event.

Previous reports concerning intratympanic gentamicin in the treatment of Meniere's disease have included data concerning pretreatment and post-treatment caloric activity using ENG caloric tests. Table II shows the ENG caloric findings after treatment in studies involving more than 15 patients. In general, the timing of the post-treatment ENG, as well as the method, is not uniformly reported. For the most part, post-treatment ENG caloric tests appear to have been usually performed within the first few months of treatment and were reported as a change in ED or as the fraction of patients with absent bithermal or ice-water caloric test responses. Overall, results have tended to show variable changes in ENG caloric test responses after treatment.

Results from the present study seemingly demonstrated variability in the effect of intratympanic gentamicin clinically and with respect to a change in caloric ED among the individuals treated. Although most of our patients developed convincing evidence of ototoxicity, some did not. Several factors might explain this, including the following:

1. Possible differences in the position of the tympanostomy tube, the size of the myringotomy incision, and failure to use tragal pressure to "pump" the drops down the ear canal through the tube may have resulted in different amounts of gentamicin reaching the middle ear and thus accumulating in the round window niche.
2. Factors affecting middle ear contact time (e.g., patency of the eustachian tube, vascularity of the middle ear mucosa, the presence of inflammation).
3. The anatomy of the round window niche and barriers to the inner ear absorption (i.e., mucosal webs, thickness of round window membrane, and different diffusion characteristics across the round window membrane).
4. Variable rates of metabolism and clearance of gentamicin from the inner ear.
5. Variable susceptibility of an individual to aminoglycosides (i.e., the genetic predisposition of an individual).

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Whether patients with ears affected by Meniere's disease might be more sensitive to the effects of topical gentamicin compared with so-called normal subjects cannot be answered at present. Although no specific human data are available to answer this question, extrapolation from an animal study by Kimura et al.[21] demonstrated that chinchillas with hydropic ears appeared more sensitive to the effects of aminoglycosides than did their control animals.

In the present study we also observed worsening of hearing in 10 of the patients according to 1995 AAO-HNS CHE criteria in the short term (patient 5 also developed a sensorineural hearing loss mostly in the higher frequencies greater than 4 kHz). When interpreting these results, several considerations must be taken in account. Assuming that some patients had worsening of hearing from topical therapy, it should be possible to perform sequential audiograms in the future, to determine whether the observed cochlear ototoxicity was permanent or reversible. For example, Kaplan et al.[13] demonstrated that 7 of 29 (24%) patients with hearing loss 1 month after treatment following fixed-schedule intratympanic administration of 19 mg/mL concentrated topical gentamicin recovered hearing to pretreatment levels over time. Moreover, changes in hearing might also reflect the expected fluctuation in hearing seen in Meniere's disease and not a direct drug effect. This latter point might conceivably explain the improvement in hearing identified in patients 10 and 15. Nonetheless, 9 (45%) of our patients developed both a hearing loss and a significant caloric test reduction, implying that there was a simultaneous effect of gentamicin on both the cochlea and the labyrinth.

When a solution for ablation is delivered directly into the middle ear by either a transtympanic injection or a catheter route, one can be certain that it reaches the middle ear. Using our protocol, we initially wondered whether the drops would actually pass through the tympanostomy tube and reach the middle ear. Our findings most assuredly demonstrate that this method (not dissimilar to instructions for topical use that would be normally provided to patients for treatment of external and middle ear infectious or inflammatory diseases) is quite effective for the delivery of drops into the middle ear, a cautionary point that should not be taken for granted when topical gentamicin- or other aminoglycoside-containing drops, with their recognized potential for ototoxicity, are prescribed for treatment of middle ear sepsis in the presence of a TM defect.

Although the gentamicin concentration in the ototopical preparation that was used was only 3 mg/mL (approximately 10 times less than in some of the solutions used in previous studies), the ototoxic effects were apparent both clinically and quantitatively, as measured by pretreatment and post-treatment ENG caloric tests. The comparatively long duration of continued exposure presumably allowed for the concentration of gentamicin to occur within the inner ear, which resulted primarily in vestibulo-ototoxic effect with some patients having cochlear ototoxicity despite the small volume received each time the drops were applied (approximately 0.10–0.15 mL).

Because the topical drops in the present study contained betamethasone in addition to gentamicin, one might wish to consider what the contribution of the steroid component was, if any, in the development of ototoxicity? Limited data are available regarding the effect of intratympanic steroids, which in some animal studies have shown them to be possibly cochleotoxic.[22–24] To date, there are no reports that have conclusively demonstrated ototoxic effects of intratympanic steroids in humans. In one series, intratympanic steroids appeared to have been beneficial in patients with presumed immune-mediated hearing loss (i.e., sudden sensorineural hearing loss and in Cogan's syndrome).[25] However, whether this form of treatment may be beneficial in endolymphatic hydrops remains controversial.[25,26]

In previous studies from our institution, patients with suspected inadvertent topical ototoxicity from commercially available gentamicin-betamethasone appeared to develop primary vestibulo-ototoxicity around treatment day 20 on average (range, 7–56 days of treatment), typically from the start of therapy for treatment of chronic suppurative otitis media or otorrhea after tube placement.[16,27] In the present study, all patients treated with unilateral Meniere's disease had dry ears at the beginning. Symptoms of ototoxicity clinically occurred by history around day 15 on average. This possibly suggests that inflamed, hypertrophic middle ear mucosa with purulent debris and so forth may have afforded some protection to round window initially, thus delaying the onset of topical ototoxicity in the two groups. Therefore, we think our study continues to demonstrate on clinical grounds further dangers for ototoxicity with the prolonged use of commercially available topical gentamicin preparations.

To date, we have found this particular protocol of administering topical gentamicin into the middle ear to be convenient for both the patient and the physician. Insertion of a tympanostomy tube is a procedure that is mastered by all otolaryngologists, tolerated well by patients as an office procedure, and proves to be cost-effective. Once the tympanostomy tube is inserted, the patient is not dependent on the physician for treatment, which may be a significant advantage, especially in underserviced regions. As with most drug therapy, it is suitable for a compliant patient who understands how to apply the drug and when to stop its use.

CONCLUSION

The present study clearly demonstrates that in the presence of a tympanostomy tube, commercially available gentamicin-containing eardrops penetrate the middle ear cavity, where they can be absorbed into the inner ear, resulting primarily in a vestibulo-ototoxic and, in some instances, a cochleo-ototoxic effect, or both. We conclude this particular protocol to be a simple, convenient, and effective method for applying gentamicin intratympanically for patients with Meniere's disease. Success in the treatment of Meniere's disease according to the 1995 AAO-HNS CHE recommendations (i.e., vertigo control, preservation of hearing, and so forth) cannot be evaluated in the present study and must be assessed after a minimum follow-up of 2 years.

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In addition, the present study offers further support regarding the primarily vestibulo-ototoxic nature of commercially available eardrops containing gentamicin when used in a prolonged fashion. Physicians are again cautioned to frequently assess the need for preparations with topical gentamicin and, for that matter, all aminoglycoside-containing drops in the presence of a TM perforation or defect and to stop the drops immediately when discharge from the ear ceases or the middle ear becomes dry, to prevent their further absorption through the round window membrane into the inner ear.

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