Systemic absorption of gentamicin nasal irrigations

W. Stites Whatley, M.D., Rakesh K. Chandra, M.D., and C. Bruce MacDonald, M.D.

ABSTRACT

Objective: *To determine if gentamicin nasal irrigation is systemically absorbed, and to identify any ototoxic side effects related to its use.*

Design: *Retrospective review of 12 patients treated with gentamicin nasal irrigations (30 cc of 80 mg/L solution used bilaterally twice daily).*

Methods: *Serum gentamicin levels were assayed after the course treatment. Pure tone audiometry (250–8000 Hz) and distortion product otoacoustic emissions (DP-OAEs) at 7280, 5133, 3640 and 2560 Hz were obtained before and after therapy.*

Results: *Twelve patients (age 4 to 74, mean 43) with chronic rhinosinusitis were treated for 3–15 weeks (mean 7 weeks). All patients had undergone previous endoscopic sinus surgery. Ten patients had pretreatment cultures that grew organisms sensitive to gentamicin (*Pseudomonas, Proteus, *or methacillin resistant* Staphylococcus aureus*), and three patients had cystic fibrosis. Ten of 12 patients (83%) had detectable posttreatment levels of gentamicin, with a mean serum level of 0.42 mcg/mL (range 0.3 to 0.7 mcg/mL). Four of 12 patients (33%) had serum gentamicin levels within the normal range for gentamicin trough (0.5 to 2 mcg/mL). Comparison of pre- and posttreatment audiologic data revealed no significant change in PTA or DP-OAE, except for the right ear at 8000 Hz on PTA ($p = 0.035$) where a mean of 7 dB loss was observed. No patient reported hearing loss or vertigo during treatment.*

Conclusion: *Gentamicin nasal irrigation may be systemically absorbed. Although the otologic consequences of this finding are questionable, patients receiving gentamicin nasal irrigations should be counseled regarding this hypothetical possibility.*

(Am J Rhinol 20, 251–254, 2006; doi: 10.2500/ajr.2006.20.2855)

Topical antibiotic therapy in patients with refractory sinusitis has been shown to improve pain, mucosal edema, secretions, and postnasal drip[1] and has been useful after endoscopic sinus surgery.

Topically administered aminoglycosides such as gentamicin have the possible advantages of targeting organisms that may be resistant to oral antibiotics while delivering drug directly to the site of infection or bacterial colonization. Because the rate and extent of bacterial kill with aminoglycosides are a function of drug concentration and are not time dependent,[2] topical delivery also offers the theoretical advantage of a high drug concentration in the targeted tissues without the complications of systemic therapy. Rubenstein[3] evaluated the systemic absorption of nasally administered gentamicin in healthy volunteers, where serum levels were detectable when the drug was dissolved in 1% sodium glycocholate but undetectable when dissolved in saline. The pharmacokinetic profile of topical gentamicin in chronic sinusitis patients' status post–endoscopic sinus surgery, however, has not been addressed in the literature. Thus, we conducted a pilot investigation to determine (1) whether potential exists for systemic absorption of gentamicin irrigations and (2) if any evidence of ototoxicity could be detected when this therapy is applied in patients with persistent exacerbation of chronic sinusitis.

METHODS

Twelve consecutive patients with persistent purulent exacerbation of chronic sinusitis after systemic antibiotic therapy and endoscopic sinus surgery were prospectively enrolled from the Nasal and Sinus Clinic at the University of Tennessee Health Science Center. In 10 patients, endoscopically guided cultures showed sensitivity to gentamicin. In two patients, repeated cultures were negative despite clinical evidence of purulent secretions, and topical gentamicin was prescribed empirically in those cases. Criteria for exclusion from the study included the presence of middle ear disease and medication noncompliance.

Patients were instructed to perform positive pressure bulb irrigation twice daily with 30 mg of gentamicin solution to each nasal cavity. The concentration used was 80 mg of gentamicin per liter of normal saline. Patients were followed clinically every 1–2 weeks where they were questioned regarding medication compliance, sinonasal symptoms, hearing loss, and balance complaints. Nasal endoscopy was performed at each visit, and topical gentamicin irrigation was continued until purulent secretions were no longer observed. Baseline pure tone audiometry and distortion product otoacoustic emissions (DP-OAEs) were performed before the initiation of therapy and repeated within 12 hours of the last treatment dose. According to the protocol, any reports of hearing loss or tinnitus during therapy were to be evaluated by repeat audiologic testing with discontinuation of therapy for any deficit from baseline. Similarly, any balance complaints were to be investigated by rotational chair testing, with discontinuation of treatment where appropriate. To confirm normal middle ear status, otoscopy was performed at each clinical visit and tympanometry was performed as part of each audiologic evaluation. Pure tone thresholds were determined using a GSI 61 clinical audiometer with Telephonics TDH-50 headphones. The audiometer was calibrated to the American National Standards Institute 1996 standards from 125 to 8000 Hz. The DP-OAEs were obtained in a quiet room using the computer-based Bio-logic Systems Corp. Scout Sport system and software (590-OAUM03). DP-OAEs were obtained by presenting two pure tone signals simultaneously at two different frequencies (f1 and f2, where $f2 > f1$ and $f1 = 65$ dB SPL and $f2 = 55$ dB SPL). DP-OAEs (2f1-f2) were

From the Department of Otolaryngology–Head and Neck Surgery, University of Tennessee, Memphis, Tennessee
Address correspondence and reprint requests to Wesley Whatley, M.D., University of Tennessee, 956 Court Avenue, Memphis, TN 38163
E-mail address: wwhatley@midsouth.rr.com

measured in each ear as a function of the geometric mean of primary tones at 2566, 3640, 5133, and 7288 Hz. The data are reported as a DP gram. The DP gram is comparable with the traditional audiogram but provides a measure of outer hair cell function not hearing.

A serum gentamicin level was obtained in all patients within 12 hours of the final topical gentamicin dose. Blood was drawn and sent to Laboratory Corporation of America, Kansas City, MO, where it was evaluated using the fluorescence polarization technique.[4] Values were determined using a standard curve calibrated from reference standards ranging from 0 to 10 μg/mL, and all results were verified by repeat testing. Gentamicin levels were reported in micrograms per milliliter with a normal peak serum value of 6–10 μg, a normal trough value of 0.5–2 μg, and a lower limit of detectability of 0.14 μg/mL.

Statistical analysis was performed using SAS JMP 5.1 software (SAS Institute, Inc., Cary, NC) using multiple two-tailed paired *t*-tests. Pre- and posttreatment pure tone thresholds were compared at all tested frequencies, and pre- and posttreatment DP-OAE's were compared at four frequencies (2566, 3640, 5133, and 7280 Hz). Proportions were analyzed using the Fisher's exact test. Statistical significance was considered as $p \leq 0.05$.

Table 2 **Mean pre- and posttreatment thresholds**

Frequency (Hz)	Pretreatment (±SEM)	Posttreatment (±SEM)	Paired *t*-test (*p* value)
Right Pure Tone (dB HL)			
250	18 (2.97)	18 (3.17)	1
500	16 (3.01)	15 (2.35)	0.46
1000	18 (5.11)	18 (5.35)	1
2000	17 (5.31)	17 (4.65)	1
4000	30 (8.42)	30 (8.55)	0.34
8000	37 (9.05)	44 (9.43)	0.035*
PTA	17 (4.34)	17 (4.04)	0.71
Left Pure Tone (dB HL)			
250	20 (3.22)	19 (2.91)	0.79
500	16 (3.78)	19 (3.40)	0.166
1000	20 (4.82)	20 (4.93)	1
2000	19 (5.10)	21 (5.20)	0.26
4000	29 (8.52)	29 (8.60)	1
8000	39 (8.55)	39 (8.91)	0.79
PTA	18 (4.46)	20 (4.42)	0.15

HL = hearing loss; PTA = pure tone average.
**Statistical significance: $p < 0.05$.*

RESULTS

Patient characteristics and serum gentamicin levels are given in Table 1. Audiometric data are summarized in Table 2.

The study consisted of seven women and five men, aged 4–74 years (mean, 43 years). No patient developed cochlear or vestibular complaints during treatment, and all patients underwent pre- and posttreatment pure tone audiometry. All patients received pre- and posttreatment DP-OAEs, except patients 10 and 12, who had no pretreatment OAE data. Posttreatment DP-OAEs were normal in both of these patients. A serum gentamicin level, drawn within 12 hours of the last dose, was recorded in all patients after completion of therapy. All patients had previous endoscopic sinus surgery, and the interval between most recent surgery and the initiation of gentamicin therapy ranged from 5 to 334 days (mean, 69 days). Underlying significant comorbidity included cystic fibrosis in three patients, sarcoidosis in one patient, and inverting papilloma in one patient. Pretreatment endoscopically directed cultures were obtained in all patients, and 10 of 12 cultures showed organisms sensitive to gentamicin. In two patients, repeated cultures revealed no growth despite persistence of purulent collections observed endoscopically. These patients were treated empirically with the intent of covering organisms that are commonly implicated in our postsurgical exacerbations, *viz., Staphylococcus* and *Pseudomonas.* The

Table 1 **Characteristics of the study group**

Patient Number	Age	Sex	Cultured Organisms	Length of Therapy (wk)	Post-treatment Serum Gentamicin Level (μg/mL)
1	50	F	Treated empirically	12	0.001
2	74	F	*Pseudomonas aeruginosa*, *Staphylococcus aureus*	7	0.60
3	47	M	*Staphylococcus aureus*	12	0.30
4	65	M	Proteus	6	0.60
5	15	F	*Pseudomonas aeruginosa*	6	0.40
6	43	F	Treated empirically	2	0.70
7	49	F	β-Hemolytic streptococcus	5.5	0.30
8	4	M	*Pseudomonas aeruginosa*	7	0.30
9	72	F	*Staphylococcus aureus*	3.5	0.00
10	50	F	*Staphylococcus aureus*	5	0.40
11	33	M	*Bacillus* sp.	3	0.30
12	12	M	*Pseudomonas aeruginosa*	15.5	0.30

length of treatment ranged from 2 to 15 weeks (average, 7 weeks) as was dictated by endoscopic resolution of the disease process.

Ten of 12 patients (83%) had detectable posttreatment serum gentamicin levels, ranging from 0.3 to 0.7 μg/mL, with a mean level of 0.42 μg/mL for patients with detectable levels. Four of 12 patients (33%) had serum levels within the normal range for gentamicin trough (0.5 to 2 μg/mL). Gentamicin levels exhibited no correlation with any of the following variables: patient age, sex, body mass index, length of treatment, or interval between most recent surgery and the initiation of treatment.

Audiologic testing data are summarized in Fig. 1 and Table 2. Comparison of pre- and posttreatment audiometry was performed for each available frequency (250, 500, 1000, 2000, 4000, and 8000 Hz), pure tone average (500, 1000, and 2000 Hz), and DP-OAE at four GM frequencies (2560, 3640, 5133, and 7280 Hz). Data for each ear were evaluated separately. This analysis revealed no statistically significant changes in pure tone data or DP-OAE, except for the right ear at 8000 Hz ($p = 0.035$), where the mean pretreatment threshold was 37 dB versus 44 dB after therapy. For this variable (right ear, 8000 Hz) 7 of 12 (58%) patients experienced a threshold increase of $\geq$5 dB. In 5 of 12 (42%) patients the threshold increased by at least 10 dB, and one patient (patient 10) experienced a threshold shift of 30 dB at 8000 Hz. Despite a posttreatment threshold of 50 dB at 8000 Hz, her posttreatment DP-OAEs were normal at all frequencies. This patient was treated for 5 weeks, and her posttreatment serum gentamicin level was 0.40 μg/mL. The findings in this patient were verified by repeat audiometry and persisted 1 month posttreatment. Excluding this patient, the mean pretreatment right ear 8000-Hz threshold was 39 dB, compared with 43 dB after therapy. Interestingly, only 2 of 12 (17%) left ears exhibited a threshold increase at 8000 Hz (both by 10 dB). This significantly differed from the 58% observed in right ears ($p = 0.035$). Across the entire study group, no correlation was observed between any audiometric variables and posttreatment gentamicin levels.

DISCUSSION

Aminoglycosides function by binding the bacterial 16S ribosome unit, with rapid bacteriocidal effect. Their antibacterial activity is limited to Gram-negative organisms and some Gram-positive cocci including *Staphylococcus aureus*, but with the notable exception of *Streptococcus pneumoniae.* Additionally, aminoglycosides have no activity against anaerobes. These drugs typically are administered i.v. and have limited enteral bioavailability because of poor gastrointestinal absorption. Gentamicin is known to be vestibulotoxic and cochleotoxic when given systemically and when presented to the middle ear. The pathology of cochlear toxicity involves injury to the outer hair cells at the basal turn of the cochlea, and the vestibular pathology is found in the crista ampullaris of the semicircular canals.[5] Although gentamicin is more vestibulotoxic, high-frequency hearing loss often is the first clinical sign of aminoglycoside ototoxicity. Objective evidence of ototoxicity may be discovered by vestibular testing, pure tone audiometry, and/or otoacoustic emissions, and various protocols have been described to monitor otologic status during i.v. therapy. High-frequency audiometry (8000–20,000 Hz) has been shown as a sensitive measure of aminoglycoside ototoxicity before symptomatic changes in the speech frequencies,[6] and some of these screening protocols have shown presymptomatic effects in frequencies as low as 4000 Hz.[7] More recent studies have shown that abnormalities of DP-OAEs may correlate with cochlear damage in the ultrahigh-frequency range, before clinically measurable changes in hearing.[8] Data further suggest that DP-OAEs may be more sensitive than pure tone average in detecting minor cochlear dysfunction after gentamicin exposure. Studies have established that the incidence of ototoxicity with systemically administered gentamicin is as much as 20%,[9] particularly when these more-sensitive testing methods are used.

In this investigation, topical gentamicin irrigation was associated with detectable serum levels in 10 of 12 (83%) patients. Although all of these levels were less than or equal to the upper limit of normal for a gentamicin trough, the findings suggest that significant potential exists for systemic absorption. However, the mechanism by which drug enters the serum remains unclear from this pilot investigation. Potential pathways include translocation across mucous membranes or gastrointestinal absorption of swallowed drug. Approximately 3% of orally administered aminoglycosides are absorbed,[10] but given the relatively large volume of irrigant (30 cc per side twice daily), it is possible that the gastrointestinal route contributes to serum levels. Mucosal absorption may

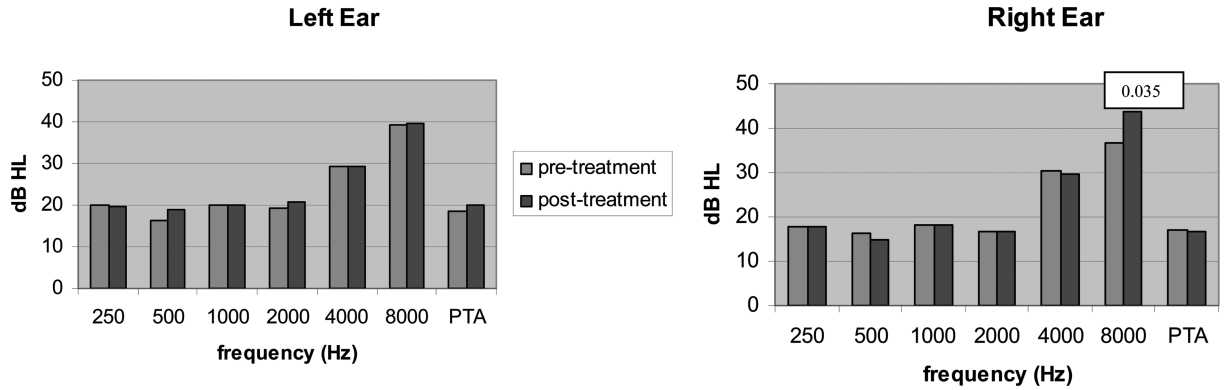

Figure 1. Frequency-specific, pre and post audiometric data for the left and right ears. A significant difference was observed in the right ear at 8000 Hz. PTA = pure tone average.

occur *via* the sinonasal and/or middle ear mucosa, and middle ear application previously has been associated with systemic levels. Lancaster *et al.*[12] detected serum gentamicin in 7 of 26 (26%) patients being treated for chronic otitis media with Gentisone HC otic drops (3 mg/cc). Although the concentration of gentamicin in an 80-mg/L nasal irrigation is far less, 30 cc of this solution delivered bilaterally has a threefold greater amount of total drug than would be in 0.5 cc (a relatively large dose) of Gentisone HC otic drops. Furthermore, the sinonasal mucosa has significantly greater surface area for absorption than the middle ear, and solution also may have collected dependently in the maxillary sinuses after irrigation, increasing the contact time available for mucosal translocation. Although the mechanism of absorption remains speculative, the preponderance of data thus implicates mucosal absorption as the most likely route.

Audiologic testing revealed a significant difference in pre- and posttreatment threshold at 8000 Hz in the right ear, and shifts of at least 5 dB were observed more often in right ears. Although these observations may have been skewed by data from patient 10, the findings do introduce the question of whether head positioning during irrigation or application with the right hand (all patients were right handed) may have preferentially allowed irrigant to enter the right middle ear with unilateral ototoxic effect. This hypothesis is supported by the observation that patient 10 exhibited a flattened right tympanogram during a follow-up audiologic battery performed shortly after saline irrigation. The influence of positive pressure bulb irrigation on middle ear dynamics may be elucidated by additional studies in which patients are evaluated otoscopically (or with tympanometry) immediately after saline irrigation and queried with respect to the character (*i.e.*, ear fullness) and laterality of otologic symptoms during irrigation. Three other limitations of this study should be noted. First, no patient in this study developed balance symptoms at any time during treatment and thus no patient underwent objective vestibular testing. Consequently, it is possible that low-grade bilateral vestibulotoxicity may have occurred but went unnoticed by patients. Second, all patients in this study had active sinonasal disease such that the dynamics of mucosal absorption of topically administered antibiotics may have been affected by the inflammatory character of the mucosal lining. Finally, statistical analysis was limited by the sample size, and it is possible that larger (or smaller) differences would have emerged with a larger study group. Nonetheless, the findings in this study indicate that topical sinonasal gentamicin irrigation may be associated with low-level systemic absorption and that additional studies are necessary to determine if this treatment modality is associated with otologic side effects. We suggest disclosing the remote but theoretical risk to the patient and advising the patient to notify the otolaryngologist for any symptomatic hearing or balance changes. Although not borne out explicitly in this pilot investigation, it would seem prudent at least to obtain baseline audiometry including the 8000-Hz frequency and to repeat this testing at the conclusion of therapy, or monthly in cases where prolonged treatment is undertaken. Any patients who are symptomatic or who have audiometric changes should undergo DP-OAEs and/or vestibular testing. The pharmacokinetics of topical administered antibiotics in the sinonasal tract remains an area of active investigation.

REFERENCES

1. Desrosiers MY, and Salas-Pranto M. Treatment of chronic rhinosinusitis refractory to other treatments with antibiotic therapy delivered by means of a large-particle nebulizer: Results of a controlled trial. Otolaryngol Head Neck Surg 125:265–269, 2001.
2. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 39:650–655, 1995.
3. Rubinstein A. Intranasal administration of gentamicin in human subjects. Antimicrob Agents Chemother 23:778–779, 1983.
4. Dandliker WB, et al. Quantification of the antigen–antibody reaction by the polarization of fluorescence. Biochem Res Commun 5:299–304, 1961.
5. Hawkins JE, and Johnson LG. Histopathology of Cochlear and Vestibular Ototoxicity in Laboratory Animals in Aminoglycoside's Ototoxicity. Boston: Little, Brown and Co., 175–198, 1981.
6. Fausti SA, Henry JA, Shaffer HI, et al. High-frequency audiometric monitoring for early detection of aminoglycoside ototoxicity. J Infect Dis 165:1026–1032, 1992.
7. Cheung R, Clark P, Nicholson PW, et al. Screening for aminoglycoside auditory toxicity in the old. Br J Clin Pharmacol 30:1–11, 1990.
8. Arnold DJ, Lonsbury-Martin BL, and Martin GK. High-frequency hearing influences lower-frequency distortion-product otoacoustic emissions. Arch Otolaryngol Head Neck Surg 125:215–222, 1999.
9. Forge A, and Schacht J. Aminoglycoside antibiotics. Audiol Neurootol 5:3–22, 2000.
10. Rybak LP. Vestibular and auditory ototoxicity. In Cummings Otolaryngology Head and Neck Surgery. Cummings CW, Flint PW, Harker LA, et al. (Eds). Philadelphia: Elsevier-Mosby, 2933–2943, 2005.
11. Roland PS. Clinical ototoxicity of topical antibiotic drops. Otolarygol Head Neck Surg 110:598–602, 1994.
12. Chia SH, Gamst AC, Anderson JP, and Harris JP. Intratympanic gentamicin therapy for Meniere's disease: A meta-analysis. Otol Neurotol 25:544–552, 2004.
13. Lancaster JL, Mortimore S, McCormick M, and Hart CA. Systemic absorption of gentamicin in the management of active mucosal chronic otitis media. Clin Otolaryngol 24: 435–439, 1999. □