Hearing Loss in Patients With Vestibulotoxic Reactions to Gentamicin Therapy

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Objectives: To determine whether patients with vestibulotoxic reactions to gentamicin have hearing thresholds worse than predicted by distributions of better-ear hearing thresholds in people of the same age and sex in the general population, and, if so, to measure the severity and audiometric pattern of that hearing loss.

Design: Retrospective case series from previously published prospective and retrospective studies of vestibular function in patients receiving gentamicin.

Setting: Tertiary neurotological practice.

Patients: Convenience sample of 33 consecutive patients seen for objective evidence of vestibulotoxic reactions after systemic gentamicin therapy. Twenty-five of 33 patients underwent valid and complete audiometry.

Main Outcome Measures: Age- and sex-corrected better-ear pure tone thresholds, 0.5 to 6.0 kHz. The better-ear audiogram was defined in 2 ways: primarily, the audiogram of the ear with the better average threshold at 0.5, 1.0, and 2.0 kHz; secondarily, the composite audiogram taking the better threshold for each frequency.

Results: Patients exhibiting vestibulotoxic reactions to gentamicin therapy had hearing thresholds that were similar to those seen in the general population at 0.5, 3.0, and 6.0 kHz. Median thresholds were 6 to 7 dB worse than expected at 1.0 and 2.0 kHz (95% confidence intervals, 2-13 dB and 3-12 dB, respectively). The largest median difference was 15 dB at 4.0 kHz (95% confidence interval, 3-23 dB), but this difference was not significant for the more conservative composite definition of the better ear.

Conclusions: Patients with vestibulotoxic reactions to gentamicin therapy have little additional hearing loss compared with the general population. Physicians should monitor both auditory and vestibular function when aminoglycosides, especially gentamicin, must be used.

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MINOGLYCOSIDES CAN cause permanent damage to inner ear hair cells, resulting in hearing loss (cochleotoxicity) and/or vestibular disturbances such as disequilibrium (vestibulotoxicity). Gentamicin, an aminoglycoside that is widely used parenterally to treat serious infections, is considered to be more vestibulotoxic than cochleotoxic.1 Black et al2 reported a clinical series of 33 adult patients, seen at a tertiary neurotology clinic a year or more after gentamicin therapy, all of whom had disabling vestibular symptoms beginning after gentamicin therapy as well as vestibulotoxic reactions documented by objective tests of vestibulo-ocular reflex function. Twenty-seven of the 33 patients underwent audiometry, including pure-tone and speech thresholds and speech intelligibility tests; 17 of these 27 had sensorineural hearing loss thought to be attributable to cochleotoxic effects of gentamicin. However, this group was predominantly middle aged (mean age, 55 years) and male (63%); age and male sex are strong predictors of sensorineural hearing loss. In the absence of pretreatment audiometry in any of these cases, it is difficult, as Black et al2 acknowledged, to estimate the magnitude of the cochleotoxic insult.

The purpose of this study is to compare the pure-tone thresholds of these patients with vestibulotoxic reactions with population-based distributions of thresholds for American men and women in different age groups and to determine whether, as a group, these patients had worse hearing than would have been expected; if so, we determined the severity and audiometric pattern of that hearing loss. If patients with severe gentamicin vestibulotoxic reactions do not also have hearing loss detectable by conventional audi-
omometry, audiometric monitoring may not be helpful in preventing vestibulotoxic effects. Use of conventional audiometry as the sole screening mechanism for aminoglycoside ototoxicity may mislead physicians not familiar with the differential susceptibility of the auditory and vestibular systems to some ototoxic drugs.

**METHODS**

In 1990, the International Organization for Standardization published a standard method (ISO-1999) of predicting the hearing thresholds of populations of men and women of different ages, with or without occupational noise exposure. The ISO-1999 was later republished with minor changes as an American National Standard (ANSI S3.44). For estimating hearing thresholds in people who have had no occupational noise exposure but who have not been screened for nonoccupational noise exposure, head injury, and other causes of hearing loss, both standards recommend a database (Annex B) that is based on a 1960-1962 audiometric survey of the US population by the United States Public Health Service.

In this study, we have measured it both ways: first, the better ear was defined as the ear with the better pure-tone average threshold for 0.5, 1.0, and 2.0 kHz (PTA-512; this frequency combination is often used as an overall estimate of ability to hear and understand speech). Second, a composite better-ear audiogram was calculated for each patient. Each of these audiograms was then age-corrected by subtracting the median threshold for the appropriate age/sex group. Age-corrected thresholds from a group similar to the unscreened US population should be as often positive as negative (ie, the median should be zero). The 95% confidence intervals (CIs) for median age-corrected thresholds were calculated by the method described (a composite of better-ear thresholds).

**RESULTS**

Speech (spondee) thresholds should be within 10 dB of the “Fletcher average” (the average of the best 2 of the thresholds for 0.5, 1.0, and 2.0 kHz). When the speech threshold is more than 10 dB better than the Fletcher average, the validity of the pure-tone audiogram is questionable. Two of the 27 patients with audiometric data had such discrepancies and were therefore excluded from further analysis. A third patient had a mild conductive hearing loss in one ear, but her data were not excluded, because Annex B, representing the entire US population, did not exclude conductive hearing loss.

The 25 remaining patients were distributed across 12 age/sex groups; only 1 group (men aged 55-64 years) had as many as 4 patients. Audiograms for the better ears (based on better PTA-512) for these 4 men are shown in Figure 1. The figure also shows the 10th, 50th, and 90th percentiles for the same age/sex group from Annex B. The audiograms all show high-frequency hearing loss, with thresholds that are mostly between the 50th and 90th percentiles. Two patients had thresholds negligibly worse than the 90th percentile at 4.0 kHz (70 dB vs 68 dB). The third had a 2.0-kHz threshold of 55 dB (90th percentile, 43 dB) and a flat audiogram within normal limits at higher frequencies for his age/sex group.

Three of these 4 men had composite better-ear audiograms that were slightly better than the audiograms shown
in Figure 1 (at a single frequency in each case: a 5-dB shift at 0.5 kHz, a 5-dB shift at 6.0 kHz, and a 10-dB shift at 8.0 kHz). This was typical of the entire group: 86% of thresholds were unaffected by the method of better-ear definition.

Of 150 better-ear thresholds (25 patients, 6 frequencies), 21 (14%) were worse than the 90th percentiles (there was no difference between the better ears according to PTA-512 and the better ears according to composite measures). The 95% CI for this proportion extends from 8% to 21% and thus is not significantly different from the expected 10%. Seven of the 21 abnormal thresholds were at 4.0 kHz; only 1 was at 6.0 kHz.

Five patients (a 64-year-old man [shown in Figure 1]; 3 men aged 31, 50, and 74 years; and an 80-year-old woman) had thresholds more than 10 dB worse than the 90th percentiles for their age/sex groups. The 31-year-old man (Figure 2) had a mild hearing loss at 1.0 kHz in his better ear (as defined by PTA-512). The 50-year-old man (Figure 3) had a profound hearing loss with a deep notch at 4.0 kHz. The 74-year-old man had a profound high-frequency hearing loss, with 1 better-ear threshold (90 dB at 4.0 kHz) that was 16 dB worse than the 90th percentile for his age group (age 65-74 years) but within 5 dB of the 90th percentile for the 75- to 79-year-old age group. Similarly, an 80-year-old woman had a threshold of 65 dB at 2.0 kHz; this is 15 dB worse than the 90th percentile for the 75- to 79-year-old female age group, but the 90th percentiles for her actual age group would probably be considerably higher.

Age-corrected thresholds for better ears (defined by PTA-512) should cluster around 0 dB for the entire group. Figure 4 shows the median age-corrected thresholds, as well as the 95% confidence limits of the median for the entire group. For each frequency, the median was the 13th-largest value, and the CI extended from the 8th to the 18th rank-ordered values. As the previous examples suggest, this group differed from the US population primarily at 4.0 kHz (by about 15 dB), although the medians are also significantly different from 0 dB at 1.0 and 2.0 kHz. The median age-corrected thresholds for the composite better-ear audiograms were slightly better: only 1.0 and 2.0 kHz were still statistically significant, as the CI for 4.0 kHz extended from −2 to 23 dB HL.

Our primary finding was that people seen at a tertiary neurotological practice with disequilibrium and vestibular function loss caused by an adverse reaction to gentamicin have hearing thresholds that are similar to those seen in men and women of the same ages in the general population. There were no significant differences at 0.5, 3.0, or 6.0 kHz. Median thresholds were 6 to 7 dB worse than expected at both 1.0 and 2.0 kHz; these differences
were statistically significant for either definition of “better ear.” The largest median difference was 15 dB at 4.0 kHz, but because of higher variability at this frequency, this difference was significant only when better ear was defined using PTA-512, not when the more conservative composite better-ear definition was used. Using either definition, the number of thresholds exceeding 90th percentile values was slightly higher than—but not significantly different from—the expected 10%.

Many clinicians and scientists are surprised to learn that the 1960-1962 USPHS study remains the most recent audiometric survey of the US adult population to include bilateral or better-ear thresholds at frequencies up to 6.0 kHz and was thus chosen by the International Organization for Standardization and later published as an American National Standard to represent adult hearing in developed countries in the 1990s. Comparable contemporary data will be available when the National Center for Health Statistics formally reports the audiometric results of the fourth National Health and Nutrition Survey within the next few years, but preliminary analysis of subsets of the data suggests that Americans of any given age and sex today hear neither better nor worse than their predecessors.

The ISO-1999 and ANSI S3.44 offer the Annex A database as representative of the distributions of hearing thresholds for highly screened populations. We have instead used Annex B (unscreened) as it is a more representative sample of the population from which these patients were drawn. Other authors have suggested that Annex A was derived from studies that oversampled people of higher socioeconomic status (who tend to have better hearing) and that Annex B is generally more appropriate even for comparison to highly screened groups. For both men and women, averaging across 0.5, 1.0, 2.0, and 3.0 kHz, median thresholds in Annex B are worse than those in Annex A by 1 to 3 dB.

Both the median age-corrected threshold curve (Figure 4) and the most extreme case (Figure 3) show 4.0 kHz notches, as commonly seen in noise-induced hearing loss. Gentamicin and other aminoglycosides have generally been considered to affect the highest frequencies first and most severely. Fausti et al have shown that the earliest changes are seen at frequencies (9.0-16.0 kHz) above the conventional audiometric range for patients who have measurable hearing at those frequencies prior to treatment. Thus, our finding of a maximum effect at 4.0 kHz is surprising and suggests that noise may have contributed to some of the hearing loss in this patient group. Unfortunately, we do not have occupational or nonoccupational noise exposure histories for these patients.

The abnormal distributions of thresholds at 1.0 and 2.0 kHz are equally difficult to ascribe to aminoglycoside cochleotoxic effects. Only one of the 1.0-kHz thresholds and four of the 2.0-kHz thresholds were worse than 30 dB (composite better ears, prior to age correction). Some of the patients in this group were involved in litigation or disability claims, and slight exaggeration of low-frequency thresholds is quite common in such populations, even when pure tone and speech thresholds are in good agreement. It must be emphasized, however, that exaggeration, if present, would not have affected the objective vestibulo-ocular reflex tests used to document vestibulotoxic reactions.

Aminoglycosides may cause unilateral hearing loss, so our focus on better ears (required by the use of Annex B) could have missed some cochleotoxic effects. However, there were only 3 patients with PTA-512 asymmetries greater than 10 dB; these were men aged 64, 70, and 82 years. In each case, the maximum asymmetry was between 1.0 and 3.0 kHz and was 30 dB or less.

Our findings of small or negligible audiometric differences between patients with gentamicin vestibulotoxic reactions and the general population are not inconsistent with previous studies. Previous studies of gentamicin cochleotoxic effects have frequently reported hearing threshold changes that are either acute or of uncertain permanence. Most observed shifts are small (<20 dB at a single frequency), and about half are not confirmed on later audiometry. Many are probably spurious, based on test-retest variability. Only 17% of patients with cystic fibrosis who have had more than 10 prolonged courses of high-dose aminoglycoside treatment have hearing loss, defined as 2 or more thresholds above 20 dB HL; the per-course risk was less than 2%.

Nevertheless, it is surprising that people with severe vestibulotoxic reactions have so little hearing loss beyond what is expected for their age and sex. We are unaware of other studies of hearing loss in patients with confirmed aminoglycoside vestibulotoxic reaction. Our results call into question the value of monitoring audiometry for detection of early or reversible otoxic effects. Indeed, there is no evidence in the literature that clinical decisions based on audiometric monitoring prevent permanent ototoxic effects, whether cochlear or vestibular.

It should be stressed, however, that significant sensorineural hearing loss can occur as a consequence of aminoglycoside administration, particularly when risk factors (eg, renal failure) are present. Some Chinese, Semitic, Latin, and other ethnic populations may have high prevalences of mitochondrial mutations that predispose patients to severe hearing loss from aminoglycosides without vestibulopathy. People with these mutations often have relatives who have had hearing loss after aminoglycoside treatment, and it would seem wise to check the family history of hearing loss before prescribing parenteral aminoglycosides. Eventually, genetic screening with or without monitoring audiometry could be effective in preventing disabling hearing loss in such groups.

The incidence of disabling aminoglycoside vestibulotoxic reaction is unknown. In our practices, one of us (F.O.B.) focused primarily on vestibular disorders, and another of us (R.A.D.) focused primarily on hearing disorders; we have both observed that permanent vestibulotoxic reaction is many times more common than permanent cochleotoxic reaction. Patients receiving aminoglycosides should be checked frequently for symptoms of vestibular dysfunction. Monitoring using either objective or psychophysical measurement of vestibulo-ocular reflex has been recommended, but vestibulo-ocular reflex monitoring has not been shown to prevent vestibulotoxic effects. While many different bioprotective agents have been shown to reduce ototoxic effects from both aminoglycosides and cisplatin in animals, no
such strategy has been shown to be protective, while retaining desired therapeutic effects, in human clinical trials. As pointed out by Black et al., there is no completely safe dose or blood level for administering gentamicin therapy, and at present the only way to totally avoid the risk of aminoglycoside ototoxic effects is to choose other antibiotics.

CONCLUSIONS

1. There is little or no correlation between cochleotoxic and vestibulotoxic reactions owing to gentamicin therapy.

2. Treating physicians should be aware of the relative toxic effects of aminoglycosides and should obtain informed consent and perform appropriate monitoring of auditory and vestibular symptoms when aminoglycosides must be used.

3. Because aminoglycoside-induced hearing loss does occur, audiometry should be part of any objective monitoring protocol. Early detection of vestibulotoxic or cochleotoxic reactions and discontinuance of aminoglycoside therapy may increase the probability of functional recovery.

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REFERENCES


