

ORIGINAL ARTICLE

Clinical Evaluation and Early Diagnosis of Streptomycin Ototoxicity

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Objective: Despite its excellent anti-tuberculous activity, many clinicians avoid streptomycin because of potential ototoxicity. We evaluated the usefulness of early monitoring and patient education in identifying streptomycin ototoxicity and preserving cochlear and vestibular function.

Materials and Methods: Patients on streptomycin for mycobacterial diseases were enrolled. Vestibular and cochlear functions were evaluated by pure tone audiometry, otoacoustic emission, video-oculogram, and slow harmonic acceleration testing.

Results: Of 418 patients enrolled, 12 (2.9%) had vestibular toxicity with dizziness or imbalance and showed decreased VOR gain. No patient showed objective threshold shift on audiometry, although five (1.2%) complained of subjective hearing difficulty. Symptoms developed after 41.5 ± 18.7 days for vestibular and 59.6 ± 22.0 days for cochlear toxicity. At all three frequencies, the vestibular toxicity group showed significantly lower baseline VOR gain, which decreased further after streptomycin treatment. In these patients ($n = 3$), VOR gain recovered at higher (0.16 Hz) and decreased at lower (0.01 Hz) frequencies on serial testing.

Conclusion: Caution should be exercised in patients with lower than normal pretreatment VOR gain due to increased risk for ototoxicity. If ototoxicity occurs, vestibular function could be preserved by early detection and cessation of streptomycin.

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Introduction

Toxicity to the auditory and vestibular systems is a well-known common complication of treatment with aminoglycoside antibiotics. However, the precise incidence of ototoxicity remains controversial. Some researchers have reported auditory toxicity in up to 41% of subjects, [1] whereas others have reported a much lower incidence of about 7%. [2] Meta-analyses have demonstrated an approximate incidence of 5% for cochlear toxicity with multiple daily dosing of aminoglycosides, and a slightly higher 5.8% when single daily dosing is used. [3,4] Vestibular toxicity has been reported in 0 to 7% of patients receiving aminoglycosides. [5-7] In one study, three of five patients (60%) treated with streptomycin developed cochlear toxicity confirmed by pure tone audiometry. [8] However, few studies have addressed the incidence of streptomycin-induced ototoxicity.

Streptomycin is expected to play a more important role in the management of emerging multidrug-resistant mycobacteria. However, many clinicians avoid

prescribing streptomycin due to potential ototoxicity, despite its excellent anti-tuberculous activity. Because of the paucity of clinical data on streptomycin-induced ototoxicity, the aim of this study was to evaluate the usefulness of early monitoring and patient education in identifying the incidence of streptomycin-induced ototoxicity and the interval between initiating medication and onset of clinical symptoms, and to evaluate changes in the vestibulo-ocular reflex (VOR). We also wanted to evaluate whether monitoring and earlier detection could help in preserving cochlear and vestibular function in cases of ototoxicity during anti-tuberculosis treatment using streptomycin.

Materials and Methods

From July 1996 to October 2007, 418 patients diagnosed with tuberculosis, including 228 males and 190 females with mean age 44.7 years (range 5 to 88 years old, 5 patients were younger than 15 years) were enrolled into this study. Diagnoses were pulmonary tuberculosis, tuberculous arthritis, tuberculous lymphadenitis, and tuberculous meningitis. All

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patients were treated with 15 mg/kg/day of intramuscular streptomycin sulfate (CKD Streptomycin Inj.®, Chongkundang Pharm., Seoul, Korea). Any otologic symptoms during therapy were immediately referred to an otologist with cessation of streptomycin. Patients with previous middle ear diseases or sensorineural hearing loss were excluded.

All patients were given full explanation of ototoxicity prior to initiation of treatment. Patients received 14 to 180 days (mean 47.2 ± 11.0 days) of streptomycin treatment in the absence of vestibular or cochlear toxicity. Symptoms of dizziness, hearing loss, or tinnitus were reported, and after stopping medication, cochlear and vestibular functions were re-evaluated in symptomatic patients by an otologist. Streptomycin was stopped and the patient was observed in cases of evident ototoxicity. VOR was defined as a reflex eye movement stabilizing images on the retina during head movement by producing an eye movement in the opposite direction. The gain was also defined as the change in the eye angle divided by the change in the head angle during the head movement. Vestibular toxicity was defined as more than 20% decrease in VOR gain in a slow harmonic acceleration test or a positive head thrust test (HTT), and cochlear toxicity as a threshold shift of more than 10 dB on pure tone audiometry.

Patients without any vestibular or cochlear symptoms throughout the duration of treatment with ototoxicity monitoring, and completed slow harmonic acceleration (SHA) test before and during streptomycin therapy, composed the control group for comparison of VOR gain (n = 55). This study was approved by the Institutional Review Board of Inha University Hospital.

Cochlear and vestibular functions were evaluated before therapy and during treatment if vestibular or cochlear symptoms developed. All patients received pure tone audiometry, including 8,000 Hz otoacoustic emission (OAE) testing, video-oculogram (HOUSE IR/VENGTM system, EYE DYNAMICS Inc., USA), and a SHA test at 0.01, 0.04, and 0.16 Hz (System 2000TM Micromedical Technologies, USA). Thresholds of pure tone audiogram and OAE were compared between patients with suspicious cochlear toxicity and control group.

SPSS 12.0 software was used for statistical analysis, and the Mann-Whitney test and Wilcoxon rank sum test were used for comparisons. Data were represented as mean \pm standard deviation and p value less than 0.05 was considered as statistically significant level.

Results

Symptoms of vestibular toxicity were observed in 17 patients (4.2%), and among these, objective findings of vestibular toxicity were seen in 12 patients (2.9%). Five patients complained of transient unsteadiness only, without any decrease in VOR gain. We continued streptomycin in these patients and none of them showed symptoms or signs of ototoxicity. Although five patients (1.2%) complained of subjective hearing difficulty, fluctuation, or tinnitus during treatment, neither thresholds of pure tone audiogram nor OAE threshold showed significant difference between these patients and control group (Table 1). Streptomycin therapy was also continued in these patients.

Table 1. Thresholds of pure tone audiogram (PTA) and otoacoustic emission (OAE) after streptomycin treatment in patients with suspicious cochlear toxicity and control group. (Mann-Whitney U test, $p > 0.05$).

	Cochlear toxicity group (n=5)	Control group (n=55)	p value
PTA threshold change (dB)	5.3 ± 1.2	6.5 ± 1.5	0.156
OAE threshold (dB)	25.0 ± 7.5	31.0 ± 8.4	0.085

The interval between initiating streptomycin treatment and development of symptoms was evaluated. Vestibular toxicity developed in 41.5 ± 18.7 days (n = 12) after starting streptomycin, whereas the subjective cochlear symptoms manifested after 59.6 ± 22.0 days (n = 5).

Comparing VOR gain between the vestibular toxicity group and controls without vestibular or cochlear symptoms (n = 55), baseline values were significantly lower at all three frequencies in the vestibular toxicity group ($*p < 0.05$, Mann-Whitney Test, Figure 1). VOR gain was more significantly decreased at higher frequencies (0.04 Hz and 0.16 Hz) compared to the lower frequency of 0.01 Hz ($*p < 0.05$, Wilcoxon Test, Figure 2). In three patients with vestibular toxicity, serial evaluation of VOR gain was performed before the medication, immediately after ototoxicity, and 1 month after cessation of streptomycin. In these patients, VOR gain at higher frequency (0.16 Hz), but not at the lower frequency (0.01 Hz) showed a tendency to recover after cessation of streptomycin (Figure 3). None of the patients developed new symptoms of ototoxicity after cessation of streptomycin.

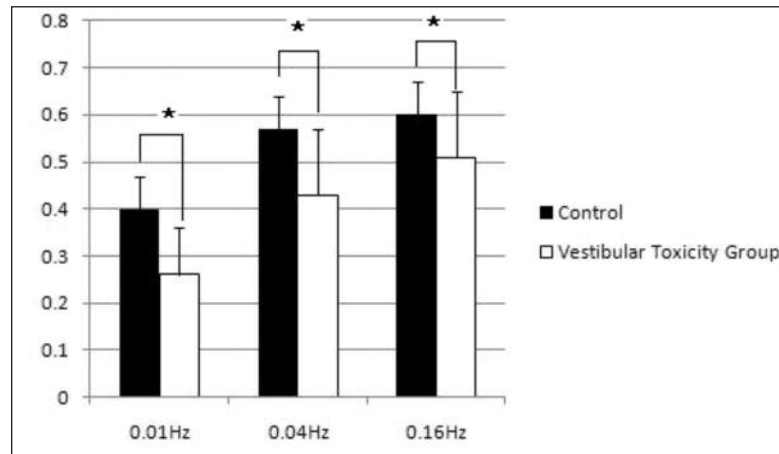


Figure 1. Baseline VOR gain was significantly lower at all three frequencies in the vestibular toxicity group. ($*p < 0.05$, Mann-Whitney Test)

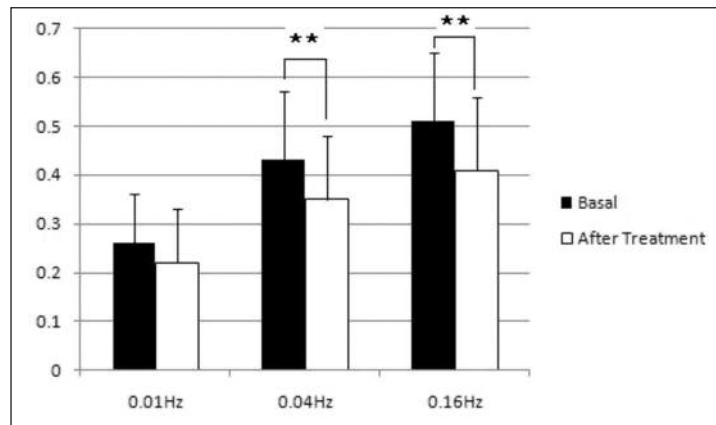


Figure 2. VOR gain significantly decreased more at 0.04 Hz and 0.16 Hz compared to the lower frequency of 0.01 Hz. ($**p < 0.01$, Wilcoxon Signed Rank Test)

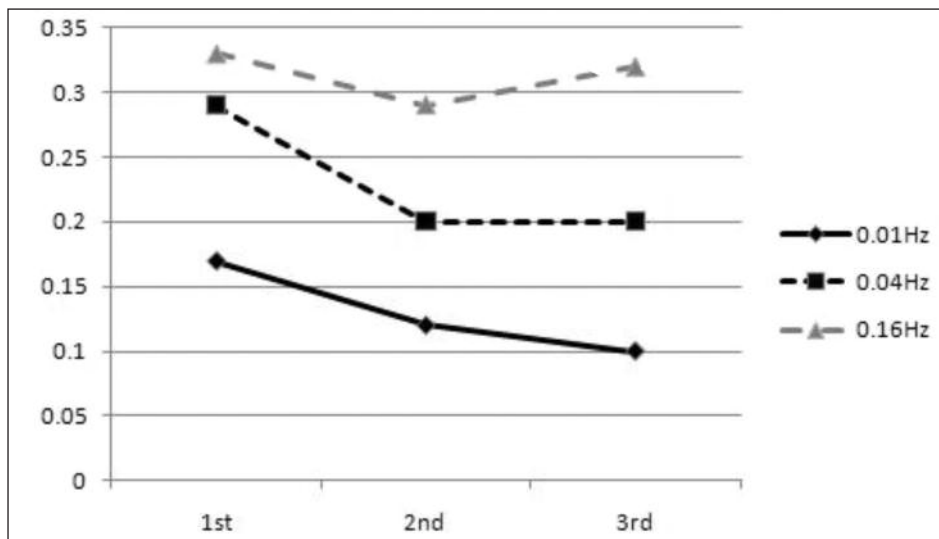


Figure 3. On serial testing of VOR gain in the patients with vestibular toxicity ($n = 3$), VOR gain recovered at higher frequency (0.16 Hz), and decreased at lower frequency (0.01 Hz). 1st: Baseline VOR gain, 2nd: VOR gain immediately after symptom onset, 3rd: VOR gain 1 month after symptom onset.

Discussion

One major irreversible toxicity of aminoglycoside antibiotics is ototoxicity, which includes drug-induced hearing and vestibular loss. Among the aminoglycosides, streptomycin and gentamicin are known to be primarily vestibulotoxic, whereas amikacin, neomycin, dihydrostreptomycin, and kanamycin are primarily cochleotoxic. Aminoglycosides induce vestibular disorders by damaging the sensory hair cells that form the peripheral sensory organ. With vestibular toxicity, the initial and most extensive hair-cell damage occurs at the apex of the crista and striolar regions of maculae. Previous studies have reported that systemic administration of streptomycin caused a dose-dependent loss of vestibular hair cells,^[9,10] and other studies have reported that the dose-dependent hair-cell loss occurs particularly in the epithelium of the utriculus, sacculus and cristae ampullaris.^[11] However, there is still no clinical data about the incidence of ototoxicity with systemic injection of streptomycin. In this study, the incidence of streptomycin ototoxicity was approximately 2.9%. Although mutations in a mitochondrial gene is accepted as a significant risk factor in aminoglycoside ototoxicity,^[12] there is still no known tendency in subpopulations. Asians might have low susceptibility to ototoxicity due to some genetic variability.

The interval between the initiation of medication and emergence of toxicity was shorter with vestibular toxicity than cochlear toxicity (41.5 days versus 59.6 days respectively) but this did not reach statistical significance.

A study of gentamicin ototoxicity using SHA testing demonstrated a universally decreased gain over the entire frequency range of testing.¹³ A prominent characteristic in gentamicin ototoxicity was a bilateral ultra-low VOR dominant time constant, but relatively maintained responses to intermediate frequency, low acceleration stimuli. The authors concluded that the gain was particularly suppressed at the lowest frequencies (0.05 Hz) and gradually increased with increasing frequencies of rotation. The decrease in VOR gain to high acceleration stimuli in comparison to intermediate frequencies may be explained by the differential effect of gentamicin, with more damage to the type I hair cells near the crest of the cristae.

However, more variable responses were recently reported by another study. These differences might be explained by different methodologies or different study populations.^[13] The tendency towards more decline in lower frequencies with relative preservation of function in higher frequencies was also observed in another study.^[14] In the current study, the vestibular toxicity group showed decreased gain before the initiation of therapy, and this decreased further at all test frequencies after streptomycin treatment. Therefore, clinicians should take more care in prescribing streptomycin in patients with low baseline VOR gain before treatment. However, the tendency of more pronounced suppression at lower frequency was not observed.

The recovery of VOR could be accomplished by central compensation in addition to recovery of peripheral vestibular function.^[18] Although the decrease of gain was observed at all frequencies, the recovery was more prominent at higher frequency (0.16 Hz). However, the clinicians should bear in mind that, because normal behavior of human being is between 1 to 5 Hz, 0.16 Hz is a relatively low frequency.^[19] In all cases, hearing was normal as tested by standard audiometry, despite vestibular dysfunction. Therefore, audiometry or subjective hearing loss cannot be used as early indicators of streptomycin ototoxicity. Moreover, although symptoms suggestive of ototoxicity may be informative when they occur, they are not reliable indicators of the onset, severity, progression, or permanence of vestibular toxicity. However, we found good correlation between streptomycin ototoxicity and decreased VOR gain in SHA test, which suggests that SHA testing is the most meaningful screening tool for streptomycin ototoxicity.

Previous studies have suggested that patients could recover from severe vestibular functional loss caused by gentamicin or streptomycin ototoxicity.^[13,14] Black and colleagues suggested that most subjects had recovery of VOR gain after loss of vestibular function.^[15] However, ototoxicity onset and recovery were independent of baseline vestibular function, and onset did not correlate with cumulative dose of the ototoxic medication. Because ototoxicity-related changes developed and continued in an unpredictable manner in relation to ototoxic drug administration, we recommend immediate discontinuation of ototoxic

medications once changes in vestibulo-ocular reflex are detected. [16,17] In this study, no patient suffered further deterioration in vestibular or auditory symptoms, or further decrease in VOR gain after stopping the medication.

In conclusion, streptomycin is still recommended as the first line choice regimen for tuberculosis. In spite of its potential to cause ototoxicity, the clinicians could use it with caution and with the aid of a well-designed system for early monitoring. Baseline values and changes in VOR gain in SHA testing would be a useful tool in early monitoring and early discontinuation of streptomycin in cases of ototoxicity.

Acknowledgements

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