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Ototoxicity screening of patients treated with streptomycin using distortion product otoacoustic emissions

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Abstract. *Ototoxicity screening of patients treated with streptomycin using distortion product otoacoustic emissions*.
Objective: Pure tone audiometry (PTA) is currently widely used to monitor ototoxicity, but this method is time-consuming. Here we validate distortion product otoacoustic emission (DPOAE) as an instrument for early detection of ototoxicity.
Methods: A cohort study was performed on newly diagnosed tuberculosis patients who were treated with streptomycin. The patients underwent hearing assessment using conventional PTA and high-frequency DPOAE (8, 9 and 10 kHz) on days 0, 7, 14, 28 and 56 of streptomycin treatment. Detection of ototoxicity according to the duration of streptomycin treatment was compared between DPOAE and PTA.
Results: Of 96 newly diagnosed patients treated with streptomycin, 50 completed the study. During the treatment period, 62.5% of the patients had vertigo, while 37.5% complained of tinnitus. DPOAE detected ototoxicity in 47.7% of the cases at day 7, 66.0% at day 14, 70.0% at day 28 and 77.1% at day 56 of streptomycin treatment. The higher frequencies were affected more by ototoxicity, with significant differences at 8 vs. 9 kHz on all testing days and at 9 vs. 10 kHz except on days 7 and 56 ($p < 0.001$). Hearing loss was detected by PTA in 2.3% of patients on day 7, in 10.6% on day 14, in 22.0% on day 48 and in 29.2% on day 56.
Conclusion: DPOAE is a sensitive tool that can detect early changes in the cochlea due to ototoxicity. Use of DPOAE rather than PTA to screen for ototoxicity could reduce screening time and would allow clinical monitoring of more patients.

Introduction

Timely identification of early changes in hearing thresholds due to drug therapy is important for preventing ototoxic hearing loss. In many cases, alternative drugs can be used or the treatment regimen can be modified if ototoxicity is detected early during treatment. Pure tone audiometry (PTA) is currently used to detect and monitor ototoxicity, but this method is both time-consuming and labor-intensive. It is essential to have an auditory detection tool that is highly sensitive and reliable, but it would be useful to have a faster audiometric test for clinical monitoring of larger patient populations. Such a test could reduce the number of patients who suffer from ototoxic hearing loss and allow patients affected by ototoxicity to retain their quality of life and avoid expensive rehabilitation.

Hearing loss from ototoxicity begins at the highest audible frequencies and progresses to the lower frequencies.[1] In addition, ototoxic drugs, particularly aminoglycosides, damage the outer hair cells of the cochlea first, followed by damage to other structures. Otoacoustic emissions (OAEs) are sounds that are generated by the outer hair cells (OHCs) within the normal cochlea.[2] Evoked OAEs represent an objective audiologic test that is noninvasive, rapid and easy to perform. Because of these properties, OAE testing is used in neonatal hearing screening programs in many centers.[3,4] The frequencies that are most commonly used for this screening procedure range from 2 to 4 kHz, an important range for speech perception and communication development in pediatric populations. However the current screening of OAEs can also detect hearing impairment at higher frequencies of up to 10 kHz.

Fausti *et al*.[1] demonstrated the need to serially monitor auditory thresholds in the high-frequency range in patients receiving ototoxic drugs.[5] In a group

of patients receiving aminoglycoside and cisplatin, Fausti *et al*.[1] reported that if only high frequencies had been monitored, early changes in auditory sensitivity would have been detected in 86.5% of the patients. The use of high-frequency tone burst-evoked auditory brainstem response (ABR) is valuable for early ototoxic detection in subjects that have previously been considered difficult to test.[1]

Monitoring the function of outer hair cells at higher frequencies (> 8 kHz) should detect hearing threshold changes before hearing loss progresses into or near the frequency range involved in speech and communication. Since some of the patients who receive ototoxic drugs are children or patients that are very ill, the monitoring method should be objective, non-invasive and rapid. A protocol defined by high frequency OAEs meets all of these criteria and may be used to detect sensory damage to the cochlea before the onset of permanent pure tone threshold shifts. The aim of this study was to validate the use of distortion product otoacoustic emission measurements (DPOAE) as an instrument for early detection of streptomycin-induced ototoxicity.

Methodology

A cohort study was performed on newly diagnosed tuberculosis patients who were treated with a daily dose of streptomycin (15 mg/kg) for two months. Patients with diseases that affected their ears were excluded from the study. The sample size was calculated using a single proportion formula based on a prevalence of ototoxicity due to streptomycin of 19%.[6] The level of confidence was set at 95%, and the level of precision was set at 10%. Therefore, 59 patients were needed for this study. Before streptomycin treatment began, otoscopic examination and tympanometry (model GSI 37 Auto Tymp tympanometer, Grayson-Stadler Inc., NH, USA) were performed. These assessments were followed by hearing assessment by PTA at frequencies of 0.5–8 kHz (Diagnostic Audiometer AD 226, Interacoustics, Denmark) in a soundproof room and by high-frequency DPOAE at frequencies of 8 kHz, 9 kHz and 10 kHz (Audx II by Bio-logic System Corporation, Illinois, USA) in a quiet room.

The study only included patients with normal hearing before therapy onset, as indicated by PTA thresholds of less than 25 dBHL and pass results for DPOAE. The examination and tests were repeated on days 7, 14, 28 and 56 of treatment. Symptoms of hearing loss, vertigo and tinnitus were documented carefully. A patient was recorded as failing the DPOAE screening when the patient did not pass two of three 8-9-10 kHz tested frequencies. Using PTA as the gold standard, hearing impairment was defined as a pure-tone threshold elevation of at least 20 dB at any frequency, or at least 10 dB at two adjacent frequencies, with regard to baseline measurement [American Speech, Language, Hearing Association (ASHA), 1994]. The time of detection of ototoxicity was compared between DPOAE and PTA. Data entry and analysis were performed using SPSS Version 11.5 software. The McNemar test was used to compare the percentage of patients who failed DPOAE at different frequencies according to the streptomycin treatment duration (days). The p-value threshold for statistical significance was set at $p = 0.001$.

Results

During the study period, there were 96 newly diagnosed tuberculosis patients treated with streptomycin. Although 70 patients consented to participate in the trial, 20 did not adhere to the follow-up schedule. The response rate was thus 71.4%, and 50 patients were included in the analysis. The age of the tuberculosis patients ranged from 15 to 66 years (mean age, 34.4 ± 12.81 years), and there were about the same number of men (n = 24; 48%) and women (n = 26; 52%) in the study. In the study cohort, 92% were Malays, 2% were Chinese and 6% were other ethnicities. This reflects the racial distribution in the study population.

Figure 1 shows the percentage of patients who developed vertigo after starting streptomycin treatment: 25% of the patients had vertigo one week after treatment onset, and this percentage increased to 62.5% after 56 days (8 weeks). Figure 2 shows the percentage of patients who developed tinnitus after starting streptomycin treatment: 16% of the patients complained of tinnitus after a week of treatment, while 37.5% had tinnitus when therapy was completed.

As shown in Figure 3, DPOAE detected ototoxic hearing impairment as early as 7 days after treatment onset in 47.7% of the cases. DPOAE detected ototoxicity in 66% of the cases on day 14 of streptomycin treatment, in 70% on day 28 and in 77.1% on day 56. PTA detected hearing loss in only 2.3% of

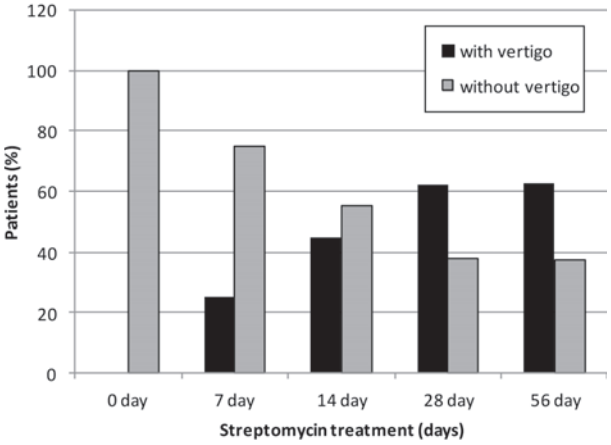

Figure 1
Percentage of patients that developed vertigo according to the number of days of streptomycin treatment.

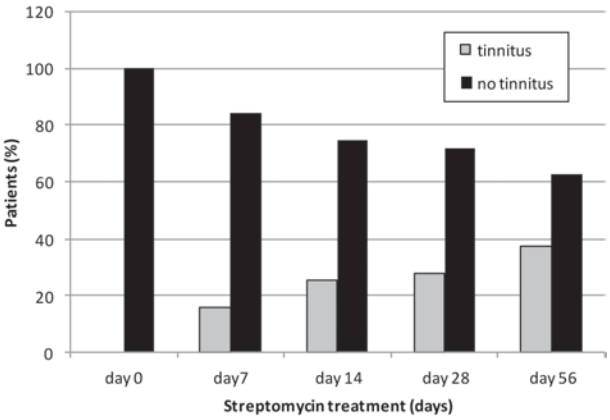

Figure 2
Percentage of patients developing tinnitus according to the number of days of streptomycin treatment.

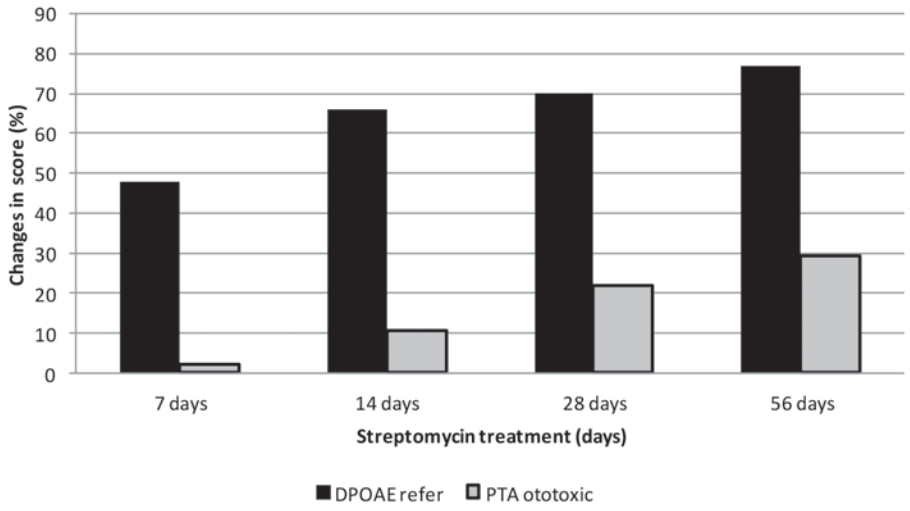

Figure 3
Changes in audiological scores on the distortion product otoacoustic emissions (DPOAE) and pure tone audiometry (PTA) tests according to the number of days of streptomycin treatment.

patients (1 case) after 7 days of treatment, in 10.6% on day 14, 22% on day 48 and in 29.2% on day 56.

Figure 4 shows the percentage of patients who failed DPOAE screening as a function of the investigated frequency (8 kHz, 9 kHz and 10 kHz). The McNemar test was used to compare the results at each frequency on each screening day. On days 7 and 56, the number of patients with a failed test at 9 kHz was similar to (day 7) or exceeded (day 56) the number of patients with a failed test at 10 kHz. However, on all of the other test days, there were significant differences ($p < 0.001$) in the percentage of patients who failed the DPOAE test at 8 kHz vs. 9 kHz as well as at 9 kHz vs. 10 kHz.

Discussion

Streptomycin, which is an aminoglycoside antibiotic, is known to cause hearing loss. Typically, once the damage is done, cochlear function cannot recover. Unfortunately, primary prevention is not always feasible; thus, early detection of ototoxicity becomes of paramount importance. Early identification of hearing loss, before significant hearing

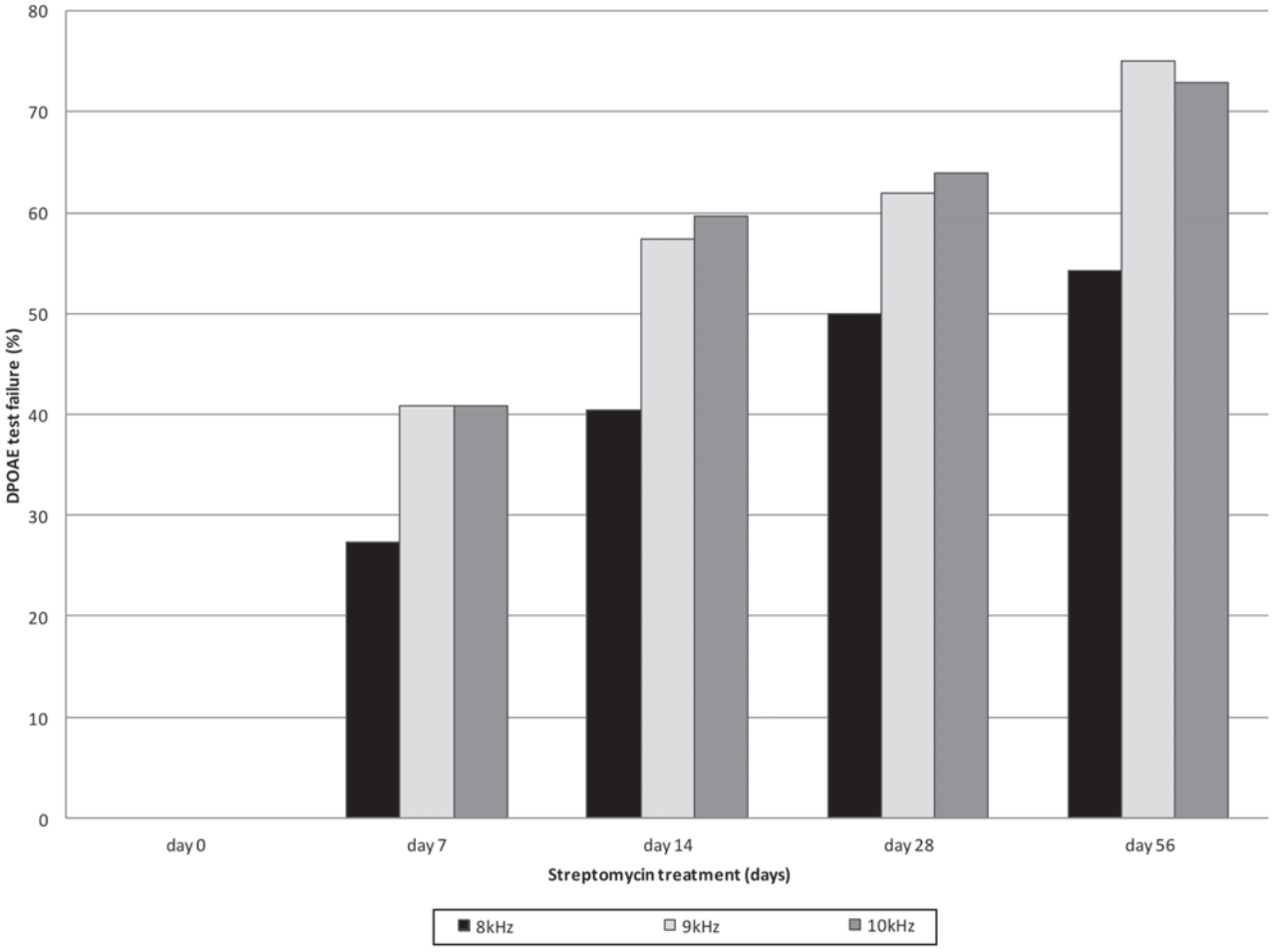

Figure 4
The percentage of patients that failed the distortion product otoacoustic emission (DPOAE) test at each frequency [significant differences ($p < 0.001$) at 8 and 9 kHz on all days; significant differences at 9 and 10 kHz except on days 7 and 56].

impairment develops over the audiometric pure-tone frequencies involved in communication, is the best way to ensure effective and timely remediation and rehabilitation.[7]

In this study, vertigo, which is a subjective complaint, was the ototoxicity symptom most frequently reported by the patients. After only one week of treatment, 25% of patients complained of vertigo; this proportion increased to 62.5% after eight weeks of treatment. Most patients were able to tolerate the vertigo and thus to continue streptomycin treatment, but two patients required a reduced dosage and, in two others, streptomycin was replaced by ethambutol. Our findings were consistent with results from some other studies. In a series of 87 patients undergoing aminoglycoside therapy, Peloquin et al. reported that nearly half experienced dizziness related to vestibular toxicity and that subjective symptoms occurred most patients.[6] In that study, the therapy needed to be stopped in two patients. In another study, Maria *et al.*[8] reported that vestibular symptoms affected 61.1% of the 36 tuberculosis patients who were treated with streptomycin for 15 days.

The incidence of streptomycin-induced tinnitus is unknown, and the relationship between drug-related changes in tinnitus and hearing status has not been fully explored. Tinnitus can occur with or without ototoxic-induced hearing loss and can be temporary or permanent. Monitoring changes in tinnitus during the course of treatment can optimize the chances of clinical intervention.[9] After vertigo, subjective tinnitus was the second most often patient-reported complaint in the present study and was noted as early as the first week of treatment (15.9% of patients). The percentage of patients reporting tinnitus had increased to 37.5% by the time treatment was completed. Katijah *et*

al.[10] reported that tinnitus occurred in about 20% of patients treated with streptomycin.

The incidence of aminoglycoside-induced hearing loss remains controversial.[11] In the present study, the incidence of hearing loss identified by PTA at the end of streptomycin therapy was 29.2%. The incidence of streptomycin-induced hearing loss reported in the literature varies from 9.2% to 36%.[6,12,13] The lower rate in some studies may be due to a shorter duration of drug administration.[13] However, streptomycin-induced hearing loss can be as high as 75%, as reported in a study in Brazil.[14] Differences in reported incidence may also be due to differences in genetic susceptibility in different populations.[15]

Clinical complaints of hearing loss are uncommon until the hearing impairment affects the speech frequency range and communication problems become significant. In our study, no patient complained of hearing impairment, a finding that is in line with a study by Kim *et al*.[16] in which only 1.2% of patients complained of subjective hearing loss following streptomycin treatment for mycobacterial disease. In contrast, Peloquin *et al*. reported that 23% of patients complained of subjective hearing loss after treatment with aminoglycosides.[6] However, in addition to streptomycin, patients treated with kanamycin and amikacin were included in that study. Amikacin is more cochleotoxic than streptomycin.

Currently, there are no universally accepted protocols or guidelines for monitoring complications in patients who take potentially ototoxic agents. Vasquez and Mattucci[17] suggested that each patient undergo a baseline hearing evaluation before treatment onset followed by a weekly hearing assessment during the treatment course. They also advised a hearing assessment up to 6 months after treatment is discontinued.

In this study, DPOAE was more sensitive than conventional PTA in detecting cochlear involvement in streptomycin-induced ototoxicity. This finding was consistent with that of Stavroulaki *et al*.,[18] who reported the ability of transient evoked otoacoustic emission (TEOAE) to reveal statistically significant decreases in mean response levels and response reproducibility before any significant changes in PTA and ABR in children receiving gentamycin for 8-29 days. In future studies, a comparison of high-frequency DPOAE and high-frequency PTA would be useful for determining the usefulness of DPOAE in detecting more early changes. As expected in cases of ototoxicity, the higher frequencies were affected more often and earlier than the lower frequencies. We hypothesize that both high and low frequencies will be equally affected when there is sufficient exposure to the antibiotic. Nevertheless, a bigger sample size is needed to confirm our findings. Loss of patients in follow-up due to the long duration of hearing studies is a major limitation of these types of cohort studies.

Several studies provide support for the use of OAEs as objective measures for ototoxicity monitoring in patients who are receiving a drug that could harm their hearing. In a Sprague Dawley rat animal model, Hatzopoulo *et al*.[19] showed there was significant reduction of the signal-to-noise ratio in most tested frequencies in the post-treatment DP-gram after treatment with cisplatin. Yilmaz *et al*.[20] showed that OAE was more sensitive than an audiogram for early identification of ototoxicity. Finally, Toral-Martinon *et al*.[21] reported that DPOAE is a rapid test for evaluating hearing loss in children and that it has a diagnostic specificity of 0.97.

Dreisbach *et al*.[22] reported that DPOAE has good repeatability even at higher frequencies and recommend its use for monitoring ototoxicity in humans. Their study revealed that high-frequency DPOAE levels varied no more than 10 dB for 87.5% and 83.1% of subjects at the 70/55 and 60/50 dB SPL stimulus level conditions, respectively. According to Reavis *et al*.,[23] the factors that affect DPOAE sensitivity include the magnitude of post-exposure threshold shifts, the degree and configuration of pre-exposure hearing loss and the high-frequency DPOAE limits present at baseline. DPOAE was found to be a good predictor of hearing changes, especially when combined with pre-exposure hearing ability testing and drug dose information.[24] Nevertheless, DPOAE does not provide information about the degree, type or configuration of hearing loss. Thus, an abnormal DPOAE result must be followed by additional testing. Furthermore, DPOAEs may produce a false negative result when the lesion is proximal to the cochlea; however, this is unlikely to occur in a case of ototoxicity.[25]

Conclusion

DPOAE is a sensitive tool for detecting early changes in the cochlea due to ototoxicity. Its use as a screening method for ototoxicity will reduce

the test time compared to PTA and would therefore allow clinical monitoring to be performed on a larger group of patients.

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