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Main Article

Assessment of aminoglycoside-induced hearing impairment in hospitalized neonates by TEOAE

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Abstract

Context Aminoglycosides, as potent bactericidal antibiotics against aerobic gram-negative infections, is still widely used, especially in NICU patients, despite their known potential ototoxic effects.

Aims To evaluate the potential of transient evoked otoacoustic emissions (TEOAEs) in early identification of decreased hearing sensitivity in hospitalized neonates receiving aminoglycosides for severe gram-negative infections.

Materials and Methods Fifty (50) neonates treated with intravenous gentamicin (5 mg/kg/day) or amikacin (15 mg/kg/day) were tested with TEOAE in the beginning and the end of aminoglycoside therapeutic course. There were 23 males and 27 females, ranging from 29 to 40 weeks (mean: 36 weeks). The treatment duration was 3–30 days (in 26 neonates up to 7 days – group A, and in 24 neonates higher than 7 days – group B).

Results In group A, no statistically significant difference in the mean response level was found between the onset and the end of treatment course ($p > 0.001$).

In group B, a statistically significant difference in the mean response level was found between the onset and the end of treatment course, especially at high frequency region ($p < 0.001$).

Conclusions TEOAE is sensitive enough to detect early aminoglycoside ototoxicity. As this test is simple to perform, non-invasive and reliable, so we suggest that TEOAE test should be performed in NICU as routine for monitoring cochlear function to prevent permanent hearing loss especially in those who are receiving aminoglycoside for more than 7 days.

Keywords Neonates · NICU · TEOAE · Aminoglycoside · Ototoxicity

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Introduction

Ototoxicity refers to the damage of the cochlea or vestibular apparatus because of an exposure to a chemical source, resulting in hearing loss or disequilibrium. Today, it is shown that many well-known pharmacologic agents have toxic effects to the cochleovestibular system. These includes aminoglycosides and other antibiotics, platinum-based antineoplastic agents, salicylates, quinine and loop diuretics.

Aminoglycosides were used successfully in the treatment of tuberculosis and gram-negative infections; however, a considerable number of treated patients were found to develop irreversible cochlear and vestibular dysfunction [1].

Although the ototoxic effects of aminoglycosides are well documented, this class of drugs is still widely used. Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus. Hearing loss can be temporary but is usually irreversible with most agents. Generally, aminoglycoside-induced hearing loss is bilaterally symmetrical, but it can be asymmetrical too.

The reported incidence of hearing loss varies from 2% to 25% [2].

This wide discrepancy is most likely due to various testing methodologies, different populations studied and varying regiments of drug dosage and duration [3].

Table 1 Sex differentiation between groups

Sex	*Group A (<7 days)		*Group B (>7 days)	
	No.	(%)	No.	(%)
Male	14	53.8	9	37.5
Female	12	46.2	15	62.5
Total	26	100	24	100

*According to the treatment duration the babies were divided into two groups: <7 days (group A) and >7 days (group B).

The usual time of onset is often unpredic, and marked hearing loss can occur even after a single dose. Additionally, hearing loss may not manifest until several weeks or months after completion of antibiotic or antineoplastic therapy.

Ototoxicity can be seen in all patient categories, including fetus, premature or full-term neonates and adults. Preterm infants are more sensitive to ototoxic effects of aminoglycoside drugs because of the anatomic and functional maturation development of their inner ear. So it is important to identify these effects at an early stage to prevent severe, long-term damage.

Prevention of aminoglycoside ototoxicity involves careful monitoring of serum drug levels, as well as hearing evaluations before, during and after therapy.

In the present study we evaluated the potentiality of TEOAE in early identification of decreased hearing sensitivity in hospitalized neonates receiving gentamicin or amikacin for newborn infections. We have measured the changes in TEOAEs at the onset and the end of aminoglycoside therapeutic course.

Our main experimental hypothesis is that the TEOAE test is a simple, non-invasive, objective and reliable method to identify aminoglycoside-induced hearing loss at an early stage to prevent severe and long-term damage of the cochlea, especially in neonates.

Table 2 Comparison of amplitude before treatment (groups A and B)

Frequency (Hz)	Group A Amplitude before treatment mean (SD) (dB/SPL)	Group B Amplitude before treatment mean (SD) (dB/SPL)
700	5.05 (4.93)	5.79 (2.76)
1,000	5.21 (4.52)	6.50 (2.79)
1,400	5.73 (4.77)	6.79 (3.11)
2,000	5.40 (4.49)	6.79 (3.63)
2,800	4.32 (4.69)	7.97 (3.65)
4,000	5.32 (6.32)	8.58 (4.21)
Mean	5.17 (3.96)	7.10 (2.82)

Materials and methods

This was a prospective study conducted for a period of 6 months from September 2005 to March 2006.

In this study, 80 neonates treated with gentamicin (5 mg/kg/day) or amikacin (15 mg/kg/day) were evaluated by TEOAE test. A TEOAE response was regarded as positive (Pass criteria) when:

- The mean amplitude of the cochlear response in dB/SPL was greater than that of the noise in the external auditory canal; and
- The signal to noise ratio of the response in 0.7, 1, 1.4, 2, 2.8 and 4 KHz band frequencies was >3 dB/SPL in at least three bands.

Among them, 50 neonates who could pass this test in both the ears were included in the study. There were 23 boys and 27 girls, ranging from 29 to 40 weeks (mean: 36 weeks).

There was no evidence of otitis media or extern or any other otological disease, and there was no family history of hereditary hearing loss, too.

Treatment duration was 3–30 days, depending on the severity of the infection [in 26 neonates: <7 days (group A), and in 24 neonates: >7 days (group B)]. The drug was injected intravenously in all cases (Table 1).

OAE recording

Neonates were evaluated by TEOAE during the first 24 hours of hospitalization in NICU (at the onset of therapy). The amplitudes of emissions in frequencies between 0.7 and 4 KHz were determined and compared with the amplitudes of emissions after treatment (within 24 hours after the last dose).

All tests were performed using the ERO-SCAN TEOAE test system (screener from Etymotic Research, Inc., Maico), which had been calibrated before the study.

TEOAEs were recorded in NICU. The Click stimulus consisted of 0.7–4 KHz frequency range, at the intensity level of 83 dB/SPL (±3 dB). The test was recorded from left and right ears during each session.

Data analysis: SPSS 11.5 for Windows software (SPSS Inc., 444 N. Michigan Avenue, Chicago, Illinois 60611, USA) was used for the statiscal analysis (Mann-Whitney rank-sum test, the Student t-test, Chi-square test, Pearson correlation and Spearman rank correlation.

Results

In group A, baseline emission responses from 0.7 to 4 KHz were obtained in all cases, and the mean responses varied

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Table 3 Comparison of amplitude after treatment (groups A and B)

Frequency (Hz)	Group A Amplitude before treatment mean (SD) (dB/SPL)	Group B Amplitude before treatment mean (SD) (dB/SPL)
700	6.53 (4.79)	3.70 (2.33)
1,000	7.23 (4.00)	3.77 (2.78)
1,400	7.76 4.39)	2.29 (4.78)
2,000	7.53 (6.07)	–1.4 (9.74)
2,800	7.73 (7.26)	–6.31 (12.63)
4,000	8.82 (6.89)	–8.33 (13.53)
Mean	7.60 (4.38)	–10.05 (6.76)

from 4.32 to 5.73 dB/SPL, with a mean of 5.17 dB/SPL (SD ±3.96).

In group B, baseline emission responses from 0.7 to 4 KHz were obtained in all cases too, and the highest responses occurred at high frequencies (2–4 KHz). The mean responses varied from 5.79 to 8.58 dB/SPL, with a mean of 7.10 dB/SPL (SD ±2.82) (Table 2).

At the end of treatment course - in group A - a progress in the amplitude of emissions was observed after termination of drug consumption [with a mean response ranging from 6.53 to 8.82 dB/SPL, with a mean of 7.60 dB/SPL (SD ±4.38)], and there was no hearing deficit after treatment ($p < 0.001$; Table 3).

But in group B (more than 7 days), decrease in the amplitude of emissions was observed after terminating drug consumption [with a mean response ranging from –8.33 to 3.77 dB/SPL, with a mean of –10.05 dB/SPL (SD ±6.76)], and a statistically significant differences in the mean response level was found between the onset and the end of treatment course in this group ($p < 0.001$; Table 3).

Discussion

Ototoxicity side-effect of aminoglycosides depends on different factors such as dosage and duration of treatment, type of aminoglycosides drug, genetic factors and pharmacokinetic condition [4].

In terms of morphology, aminoglycosides progressively destroy the sensory epithelium from basal to apical turns of the cochlea; especially susceptible are the outer hair cells (OHCs) [5–8].

This initially produces high-frequency slopping hearing loss, which can progress to lower (or speech) frequencies. Typical patients are unaware of hearing loss until deficits reach mild-to-moderate levels (>30 dB hearing level) in the speech frequencies, so awareness of ototoxic medications and use of appropriate monitoring during treatment are important to preserve hearing. Management emphasis is on prevention, as most hearing loss is irreversible. No therapy is currently available to reverse ototoxic damage.

Perhaps the most promising mechanism for chronic aminoglycoside toxicity involves iron chelation leading to production of a free-radical complex. Aminoglycoside ototoxicity is likely multifactorial, and further investigation is underway. Some studies are investigating iron chelators and antioxidants as possible agents to prevent hearing loss during therapy, while other studies are exploring forms of gene therapy as future treatment options. Currently, no treatment is available apart from amplification and cochlear implantation; therefore, prevention is most important. Prevention of aminoglycoside ototoxicity involves careful monitoring of serum drug levels, as well as hearing evaluations before, during, and after therapy.

It is well accepted that OAEs reflect some aspect of the active cochlear mechanisms which are mainly attributed to the function of the OHCs [9–12].

Therefore, OAEs should be helpful in the detection of ototoxicity, since most ototoxins predominantly affect the OHCs of the inner ear. In clinical studies Zorowka et al. [13] and Hotz et al. [14] reported that OAEs are useful for monitoring aminoglycoside ototoxicity. Animal studies [10, 15–17] have also shown that OAEs could be used to detect early stages of aminoglycoside-induced pathology [13–17].

These studies highlight a number of important aspects relating to monitoring of aminoglycoside ototoxic effects,

Table 4 Comparison of the mean amplitude of OAE responses

Frequency (Hz)	Amplitude before treatment mean (SD) (dB/SPL)	Amplitude after treatment mean (SD) (dB/SPL)	Amplitude differences pre and post-treatment mean (SD) (dB/SPL)	t-test results
700	5.05 (4.93)	6.53 (4.79)	1.48 (2.74)	$t = 3.8$; $p < 0.001$
1,000	5.21 (4.52)	7.23 (4.00)	2.01 (2.31)	$t = 6.2$; $p < 0.001$
1,400	5.73 (4.77)	7.76 (4.39)	2.03 (2.97)	$t = 4.9$; $p < 0.001$
2,000	5.40 (4.49)	7.53 (6.07)	2.13 (4.50)	$t = 3.4$; $p < 0.001$
2,800	4.32 (4.69)	7.73 (7.26)	3.40 (6.42)	$t = 3.8$; $p < 0.001$
4,000	5.32 (6.32)	8.82 (6.89)	3.50 (4.83)	$t = 5.22$; $p < 0.001$

Table 5 Comparison of the mean amplitude of OAE responses

Frequency (Hz)	Amplitude before treatment mean (SD) (dB/SPL)	Amplitude after treatment mean (SD) (dB/SPL)	Amplitude differences pre- and post-treatment mean (SD) (dB/SPL)	t-test results
700	5.79 (2.76)	3.70 (2.33)	–2.08 (2.68)	$t = 5.36$; $p < 0.001$
1,000	6.50 (2.79)	3.77 (2.78)	–2.72 (3.03)	$t = 6.22$; $p < 0.001$
1,400	6.79 (3.11)	2.29 (4.78)	–4.5 (4.17)	$t = 7.46$; $p < 0.001$
2,000	6.79 (3.63)	–1.45 (9.74)	–8.43 (8.28)	$t = 7.05$; $p < 0.001$
2,800	7.97 (3.65)	–6.31 (12.63)	–14.29 (12.18)	$t = 8.12$; $p < 0.001$
4,000	8.58 (4.21)	–8.33 (13.53)	–16.91 (12.65)	$t = 9.26$ $p < 0.001$

for example some of them reported a temporary increase in OAE amplitude occurring before reduction. This phenomenon may be the basis of the increase in OAE amplitudes reported by Zorowka et al. [13] after aminoglycoside treatment in newborns with perinatal infection. They interpreted this based on the general condition improvement of the subject over time. Based on our results according to the analysis of all data before and after treatment, there is significant difference between pre- and post-treatment amplitude of emissions in group A (Table 4). However, progress in the amplitude of emissions can be seen after terminating drug consumption, and there is no hearing deficit after treatment ($p < 0.001$). This progression is mainly caused by maturation of the inner ear, and is related to the control of underlying disease, removing of vernix and debris from external ear canal , and lowering of humidity in the ear canal.

But in group B (more than 7 days), decreasing in the amplitude of emissions can be seen after termination of drug consumption (Table 5), and more significant differences were observed at high frequencies (2, 2.8, and 4 KHz).

Figure 1 and Figure 2 shows the comparison of mean amplitude emissions before and after treatment and their differences in both groups (100 ears) for sum of three low frequencies (0.7, 1 and 1.4 KHz) and sum of three high frequencies (2, 2.8 and 4 KHz). As shown, this comparison reveals significant differences in mean amplitude emission before and after treatment in the sum of three high frequencies between group A and B (Table 6).

This fact confirms the effect of aminoglycosides in decrease of emission amplitudes-especially at high frequencies in patients who received these drugs for more than 7 days.

Since OAEs are believed to result from cochlear biomechanical processes, the reduced emissions are interpreted as sign of preclinical cochlear impairment at early stages, that could not be identified by other diagnostic modalities used in other studies.

Stravroulaki et al. (1999) designed a study to evaluate the potential of TEOAE in early identification of aminoglycoside-induced cochlear dysfunction in children (17 girls and 7 boys).

Comparison of TEOAE results with pure tone audiometry and auditory brainstem responses (ABRs) was performed at their study in order to determine if this test might provide a more reliable method of monitoring early ototoxic insults to the cochlea. In their study, 24 children (median 6.7 years) receiving gentamicin (4 mg/kg/day) for 6–29 days were included in the study. Eleven children received gentamicin for up to 7 days (group A), while 13 children underwent longer-term therapy lasting 8–29 days (group B). Their hearing was serially monitored using TEOAE and pure tone audiometry (0.25–12 KHz), or ABR for younger or non-cooperative children. TEOAE data were analyzed in terms of emission amplitude and response reproducibility as a function of frequency. The results in group A showed no significant changes in hearing levels either by pure tone audiometry ($p = 0.2$), ABR ($p = 0.3$), or TEOAEs (mean response: $p = 0.06$, reproducibility: $p > 0.05$). In group B, no significant changes in hearing levels measured by pure tone audiometry ($p = 0.1$), or ABR ($p = 0.4$), were observed. But

Table 6 Comparison of the mean amplitude variation in group A and B

Frequency (Hz)	Group A mean (SD) (dB/SPL)	Group B mean (SD) (dB/SPL)
700	1.48 (2.74)	–2.08 (2.68)
1,000	2.01 (2.31)	–2.72 (3.03)
1,400	2.03 (2.97)	–4.50 (4.17)
2,000	2.13 (4.50)	–8.43 (8.28)
2,800	3.40 (6.42)	–14.29 (12.18)
4,000	3.50 (4.83)	–16.91 (12.65)

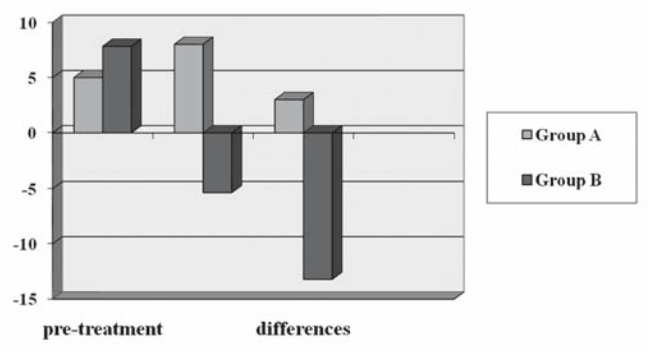

Fig. 1 Comparison of mean amplitude emissions before and after treatment and their differences in both groups (100 ears) for sum of three high frequencies (2, 2.8 and 4 KHz)

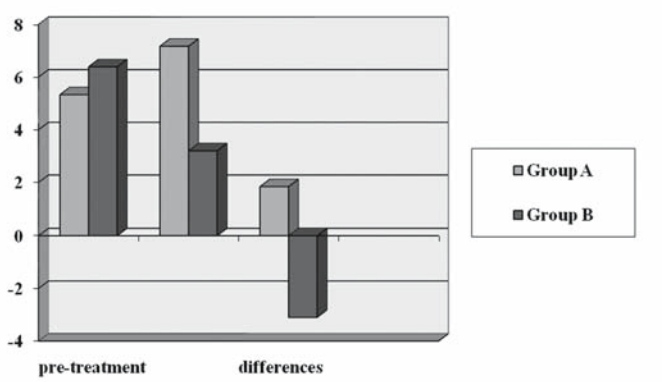

Fig. 2 Comparison of mean amplitude emissions before and after treatment and their differences in both groups (100 ears) for sum of three low frequencies (0.7, 1.0 and 1.4 KHz)

TEOAEs revealed a statistically significant decrease in the mean response level ($p = 0.017$), and in the reproducibility over the whole frequency spectrum. The findings, most likely our study, suggests that TEOAE are sensitive to minor pathology affecting the sharply tuned frequency selective mechanism of the OHCs and may be a more sensitive indicator of subtle cochlear damage than the conventional pure tone audiometry [3, 18, 19].

In another study, Hotz et al. used click and tone burst evoked TEOAEs for monitoring of ototoxicity effects on 9 patients whose individual treatment durations ranged from 9 to 33 days. They found that TEOAEs decreased when a treatment period lasted longer than 16 days. This result is consistent with our study but illustrates more delay in detecting OAE changes than our study (7 days and more), may be due to less subjects including in their study. This difference suggest that clinically we need long monitoring periods both during and after aminoglycoside treatment in order to determine the full and final ototoxic effects of a drug.

These results are most consistent with our study results and suggest that TEOAEs are sensitive enough to detect the early, subtle cochlear damage at a stage that they are still reversible.

Conclusion

TEOAE can be used as a powerful, sensitive and reliable test in evaluation of cochlear damage. As this test is simple to perform, non-invasive and reliable, so we suggest that TEOAE test should be routinely performed in NICU for monitoring of cochlear function especially in those who are receiving drug for more than 7 days, in order to prevent permanent hearing loss.

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