

Otoacoustic Emissions for Monitoring Aminoglycoside-Induced Ototoxicity in Children With Cystic Fibrosis

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Objective: To investigate whether transient-evoked and distortion-product (DP) otoacoustic emissions (OAEs) are more sensitive than pure-tone audiometry (PTA) in revealing gentamicin-induced ototoxicity in children with cystic fibrosis (CF).

Design: Prospective case-control study.

Setting: Tertiary referral audiologic center in conjunction with an academic pediatric CF unit.

Participants: The study group consisted of a consecutive sample of 12 audiologically normal children with CF and a history of gentamicin exposure (CF-gentamicin group). The control groups consisted of 8 age-matched children with CF and 11 age-matched healthy volunteers. No member of the control groups had a history of aminoglycoside exposure.

Intervention: Members of the CF-gentamicin study group received 4 mg/kg of gentamicin per day for a mean of 14.2 days (range, 11-29 days).

Outcome Measures: The PTA thresholds (250-8000 Hz) were the criterion standard. Transient-evoked OAEs' reproducibility at 5 frequency bands (800, 1600, 2400, 3200, and 4000 Hz) and total emission level were measured, as were DP-audiogram (DP-gram) amplitude (1001-6299 Hz),

input-output function dynamic range, and detection thresholds at 4004, 6006, and 7996 Hz. Baseline measurements were compared between groups examining the effect of CF and previous gentamicin exposure (2-way analysis of variance). For the CF-gentamicin group, baseline measurements were compared with those at the end of the last gentamicin treatment (paired *t* test).

Results: The PTA findings were normal for all groups at baseline and remained normal in the CF-gentamicin group after treatment. The CF-gentamicin group had significantly lower transient-evoked OAEs total emission level, DP-gram amplitude at 5042 Hz, and input-output dynamic ranges with higher detection thresholds in all frequencies compared with both control groups, which was attributed completely to previous gentamicin exposure ($P < .05$). After treatment, further decreases in total emission levels, DP-gram amplitudes (>3000 Hz), and dynamic ranges were noted, with increased detection thresholds ($P < .05$).

Conclusions: Otoacoustic emissions measurement (especially of DP OAEs) proved more sensitive than PTA in revealing minor cochlear dysfunction after gentamicin exposure. They should be used for monitoring patients receiving ototoxic factors such as aminoglycosides.

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CYSTIC FIBROSIS (CF) is a life-limiting, genetically transmitted disease characterized by abnormal transepithelial sodium and chloride transport secondary to mutations of the gene coding for the CF transmembrane conductance regulator.¹ The protean manifestations of the disease result from exocrine gland dysfunction leading to pulmonary and pancreatic insufficiency. The survival of patients with CF has improved dramatically, and now up to 80% survive to age 20 years.² This is partly owing to intensive treatment of the chronic infections that regularly threaten patients' lives. Treatment usually includes intravenous and nebulized aminoglycoside antibiotics, and the cumulative dose of these ototoxic antibiotics is quite large over

the lifetime of patients with CF. Additionally, the abnormal metabolism of these drugs in patients with CF (faster excretion with a greater volume distribution) enhances their accumulation in serum.³

Until recent years, aminoglycoside-induced ototoxicity in children could only be monitored in clinical conditions by conventional pure-tone audiometry (PTA). However, several investigators have questioned the feasibility of PTA in early detection of hearing loss and suggested the need for more sensitive and objective measures of assessing cochlear function.⁴

Evaluation of evoked otoacoustic emissions (OAEs) is becoming one of the routine audiologic testing methods, especially in neonates and children. Evoked OAEs provide a rapid, objective, reliable,

SUBJECTS AND METHODS

Children attending the CF clinic at Agia Sophia Children's Hospital, Athens, Greece, were considered for participation in the study. Entry criteria included (1) diagnosis of CF confirmed by sweat electrolyte testing; (2) age 5 years or older (responses in children younger than 5 years were considered unreliable because children this young are potentially unable to cooperate with PTA protocol); (3) normal renal function; (4) no active or recent history of otologic disease, ear surgery, head injury, or exposure to excessive noise; (5) no family history of hereditary hearing loss; and (6) normal baseline hearing (≤ 20 -dB hearing level).

Twelve of the patients with CF who fulfilled the above entry criteria had a history of intravenous gentamicin exposure for treatment of chronic infections due to *Pseudomonas aeruginosa*. These patients formed the main study group (CF-gentamicin group). During the period of chronic infection (mean duration, 6.4 years; range, 4.5-12.3 years) some patients also occasionally received other aminoglycosides (tobramycin, netilmicin). Accurate information regarding the dose of aminoglycosides for each patient is not available since treatment over the years has been administered in many different pediatric centers. The average age of the 6 girls and 6 boys in the CF-gentamicin group was 8.3 years (range, 5.2-14.1 years).

During the study period these patients received a new gentamicin regimen (4 mg/kg, 3 times daily), some in combination with antipseudomonal penicillins or third-generation cephalosporins. No patients received loop diuretics or known nephrotoxic or ototoxic drugs other than gentamicin throughout the admission. The duration of therapy ranged between 11 and 29 days (mean, 14.2 days), depending on the severity of the infection. Serum concentrations of gentamicin were measured on all patients twice

weekly. Serum trough samples were drawn immediately before the next dose, and peak samples were drawn 30 minutes after completion of the infusion/bolus dose. Trough values were routinely adjusted to concentrations between 1 and 2 mg per liter of serum, while renal function was also closely monitored and remained normal over that period (serum creatinine, <1.1 mg/dL [97.2 $\mu\text{mol/L}$]).

Two control groups were used. Because age but not sex is associated with differences in hearing in young adults,⁸ age-matched children with CF and healthy volunteers were used as controls. Eight audiologically normal, age-matched children with CF (mean age, 7.9 years; age range, 5.4-10.2 years) with no history of ototoxic drug exposure formed the CF-control group. In addition, 11 audiologically normal, age-matched children (mean age, 8.8 years; age range, 5.9-13.6 years) with no medical or family history of CF or hearing loss served as the healthy-control group.

AUDIOLOGIC PROCEDURES

Normal middle ear status was confirmed by otoscopy and standard aural immittance procedures (tympanometry with measurements of stapedial reflex thresholds) using the GSI-33 middle ear analyzer (Grason-Stadler Inc, Milford, NH). In addition, baseline PTA and evoked OAEs measurements (both TE and DP OAEs) were conducted in the children of all 3 groups. In the CF-gentamicin group, PTA and evoked OAEs measurements were repeated at the end of the last gentamicin treatment. Comparisons were performed between baseline measurements among the 3 tested groups and in the CF-gentamicin group between baseline measurements and measurements taken within 24 hours after the last gentamicin dose.

The PTA thresholds were measured using the Maico MA41 audiometer with TDH 39 headphones (Maico, Eden

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and noninvasive test for screening peripheral auditory dysfunction.⁵ Their high test-retest reliability,⁵ coupled with their accuracy and objectivity in assessing cochlear function (outer hair cell function in particular), permits their use in monitoring dynamic changes in cochlear responsiveness before these changes become functionally significant as hearing loss.^{6,7} Thus, evoked OAEs are ideal for monitoring the effects of aminoglycosides on cochlear function. The aim of our study was to investigate whether evoked OAEs (both transient-evoked [TE] and distortion-product [DP] OAEs) are more sensitive than PTA in revealing functional changes in the cochlea following ototoxic exposure in children with CF.

RESULTS

All PTA hearing thresholds were within normal limits for the subjects of all 3 groups (**Figure 1**). Furthermore, for the CF-gentamicin group, no significant threshold shifts (measured by the American Speech-Language-Hearing Association standards⁹) were noted following the last gentamicin treatment.

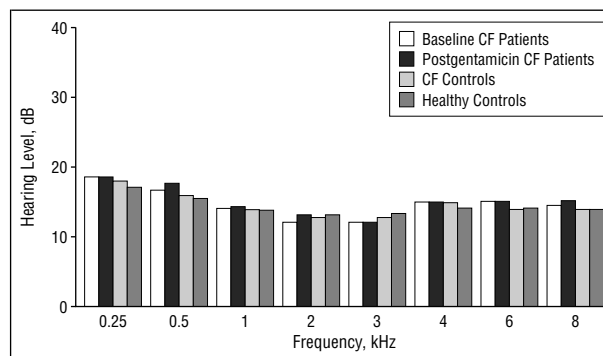


Figure 1. Pure-tone audiogram results for the children of all 3 groups. CF indicates cystic fibrosis.

In TE OAE testing, robust, well-defined responses were recorded in all children. **Table 1** lists the mean (SD) values for the baseline total emissions levels and reproducibility for each frequency band in the 3 tested groups. The baseline DP-gram amplitudes for the 3 tested groups as well as the posttreatment values for the CF-gentamicin group are shown in **Figure 2**. **Figure 3** illustrates the baseline I/O functions at 4004, 6006, and 7996

Prairie, Minn) and calibrated to AS2586 (1983 standards) from 250 to 8000 Hz (250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz). In accord with the American Speech-Language-Hearing Association standards, threshold shifts in PTA were considered significant if they showed at least a 10-dB change in more than 2 consecutive frequencies, or if 1 frequency demonstrated a change that was greater than 15 dB.⁹

Evoked OAEs were performed in a quiet, although not sound-treated, room with the children seated comfortably in lounge chairs. Transient-evoked OAEs were obtained using the computer-based ILO 88V4.2 Analyzer (Otodynamics Ltd, Hatfield, England) in the standard default mode.¹⁰ Transient-evoked OAEs were considered present when stimulus stability was better than 80% with response reproducibility more than 50% for at least 2 frequency bands. The 2 TE OAEs parameters used to compare the results were the total emission level (mean response) and the reproducibility of the waveforms in 800-Hz bands with center frequencies of 800, 1600, 2400, 3200, and 4000 Hz.

Distortion-product OAEs were obtained using the computer-based ILO92 (software version 1.2; Otodynamics Ltd) that has been described in detail elsewhere.¹¹ Two simultaneous pure-tone signals were presented to the ear at 2 different frequencies (f_1 and f_2 , where $f_2 > f_1$), and the $2f_1 - f_2$ cubic DP component was recorded. Distortion-product OAEs were collected in 2 formats. In the first, amplitude was considered a function of f_2 frequency at fixed stimuli levels (DP-grams). This plot is comparable to the traditional audiogram, but provides a measure of outer hair cell receptor function rather than hearing level. In the second format, amplitude of a fixed-frequency DP OAE was considered a function of primary level (input-output [I/O] functions). This plot provides an estimate of threshold (ie, the lowest stimulus level at which the DP OAEs can be detected above the noise) and DP OAEs' growth at supra-threshold levels. In the DP-grams, recordings were

obtained with a frequency ratio f_2/f_1 fixed at 1.22. Nine pairs of equal level primary frequencies ($L_1=L_2=70$ -dB sound pressure level [SPL]) were used at 3 points per octave, spanning an f_2 frequency range from 1001 to 6348 Hz. The 70-dB levels of the primary tones were used because these stimulus levels most reliably elicit DP OAEs from ears with hearing difficulties.¹² The DP-grams were not extended below 1001 kHz (f_2) because subject noise makes low-frequency DP OAEs difficult to measure. The DP-gram amplitude across the entire frequency range was determined for each patient. In the I/O format, data were obtained for f_2 frequencies at 4004, 6006, and 7996 Hz. Stimuli were incremented in 5-dB steps from 30- to 70-dB SPL. Dynamic range (amplitude of the I/O function at 70-dB SPL) and detection thresholds were determined for each patient.

STATISTICAL ANALYSIS

The researcher who performed the analysis of results (P.S.) was blinded to the participants' grouping. Measurements of the baseline TE and DP OAEs of the 3 groups were compared using 2-way analysis of variance (ANOVA), examining the effect of CF, the history of gentamicin exposure, and their interaction (between-subject factors). A separate test was performed for each dependent variable, including TE OAEs' total emission level, TE OAEs' reproducibility of the 800-Hz spectral bands, DP-gram amplitude across the entire f_2 frequency range, I/O dynamic range at 4004, 6006, and 7996 Hz, and I/O detection thresholds at the same frequencies. The magnitude of all statistically significant differences was further evaluated using the eta-squared (η^2) index and Cohen criteria.¹³ In addition, for the CF-gentamicin group, comparisons between baseline and final evoked OAEs measurements (TE and DP OAEs) were performed using the paired 2-tailed *t* test. Significance was determined at the .05 level for all statistical testing.

Table 1. Results of Transient-Evoked Otoacoustic Emissions Measurements*

Test Parameter	CF-Gentamicin (n = 24 Ears)	CF-Control (n = 16 Ears)	Healthy-Control (n = 22 Ears)
Total emission level, dB SPL	9.51 (3.05)	11.54 (2.27)	11.80 (2.47)
Reproducibility, %			
800 Hz	54.50 (32.30)	67.82 (19.58)	57.00 (28.61)
1600 Hz	85.31 (14.65)	90.76 (4.27)	91.00 (5.04)
2400 Hz	89.81 (7.16)	92.91 (5.98)	92.18 (6.07)
3200 Hz	90.95 (7.58)	91.00 (6.14)	90.11 (7.34)
4000 Hz	91.08 (8.29)	91.00 (7.05)	92.59 (6.96)

*Data are mean (SD). CF indicates cystic fibrosis; SPL, sound pressure level.

Hz for the 3 tested groups and the posttreatment recordings for the CF-gentamicin group.

Recordings of the effects of CF, history of gentamicin exposure, and their interaction on baseline TE and DP OAEs in the 3 different groups were analyzed with a 2-way ANOVA for each type of measurement. Two-way ANOVA with 1 and 59 *df* revealed that the CF factor had no effect on the total emission level. However, history of

gentamicin exposure had a significant effect ($F_{1,59}=5.551$, $P<.05$). No significant interaction between the 2 factors was observed. Therefore, patients in the CF-gentamicin group had significantly lower total emissions levels than both control groups. The η^2 index (0.086) revealed a moderately powerful relationship. Regarding reproducibility at each frequency, neither grouping factor (CF or history of gentamicin exposure) had any significant main effect. Additionally, no significant interaction between the 2 factors was observed.

Regarding DP-gram amplitudes at each f_2 frequency, 2-way ANOVA revealed that the CF factor had no effect. However, history of gentamicin exposure had a significant effect ($F_{1,59}=8.255$, $P<.05$) on DP-gram amplitude only at the highest frequency tested ($f_2=5042$ Hz). At this frequency, patients with CF and a history of gentamicin exposure had DP-grams with significantly lower amplitude than that of both control groups. The η^2 index (0.123) showed a very powerful relationship. There was no significant interaction between the 2 grouping factors.

Regarding the results for the I/O functions at each frequency, 2-way ANOVA revealed that the CF factor had no effect on either the dynamic range or the detection threshold. However, a history of gentamicin exposure had

a significant effect ($P < .05$) on both at the 2 highest frequencies tested (dynamic range, $F[6006 \text{ Hz}]_{1,59} = 8.436$ and $F[7996 \text{ Hz}]_{1,59} = 5.023$; detection thresholds, $F[6006 \text{ Hz}]_{1,59} = 7.145$ and $F[7996 \text{ Hz}]_{1,59} = 6.643$). The η^2 indexes revealed that these relationships were powerful (0.125, 0.78, 0.108, and 0.101, respectively). Therefore, patients with CF and a history of gentamicin exposure had significantly lower dynamic ranges and significantly higher detection thresholds than both control groups. There was no significant interaction between the 2 factors.

In the CF-gentamicin group, paired 2-tailed t tests were used to compare the baseline evoked OAEs recordings with those following the last gentamicin treatment. A significant decrease of the posttreatment total emission level (5.85) compared with the baseline (9.50) was noted ($t_{23} = 4.701$, $P < .005$). The strength of the relationship between gentamicin exposure and total emission level, as indicated by a point biserial correlation coefficient (r_{pb}),¹³ was very high (0.70). The differences in reproducibility were not statistically significant, although there was a modest decrease at each frequency at the end of treatment.

Regarding the DP-gram amplitude, a significant decrease was observed posttreatment for f_2 frequencies greater than 3000 Hz (**Table 2**). The strength of the relationship between gentamicin exposure and DP-gram amplitude (r_{pb}) was moderately high.

Finally, the dynamic range was significantly decreased and the detection threshold was significantly elevated (**Table 3**) at the end of the last gentamicin treatment for all 3 frequencies tested. The strength of the relationship (r_{pb}) between gentamicin treatment and both dynamic range and detection threshold was also moderate.

COMMENT

Ototoxic drugs such as aminoglycosides are essential for the prevention of life-threatening infections in patients with CF.⁹ The prevalence of aminoglycoside-induced hearing loss in these patients is not well defined, and the reported incidence varies from 0% to 39%.¹⁴⁻²² This wide discrepancy is most likely the result of diverse testing

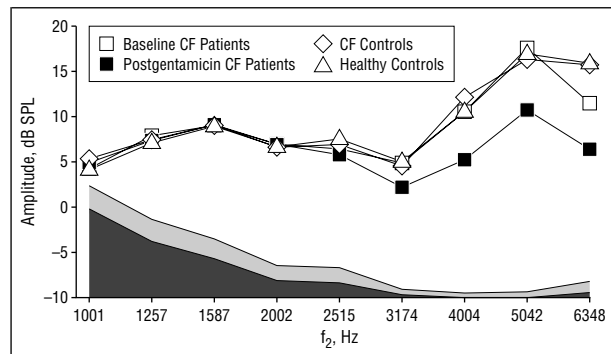


Figure 2. Mean values of distortion-product otoacoustic emissions amplitude for the children of all 3 groups. The lower shaded area represents the mean noise floor plus 1 SD, while the upper shaded area represents 2 SDs above the mean noise floor. SPL indicates sound pressure level; CF, cystic fibrosis.

methods (eg, conventional PTA, high-frequency audiometry, and auditory brainstem responses), differences of the populations studied, and varying dosage and du-

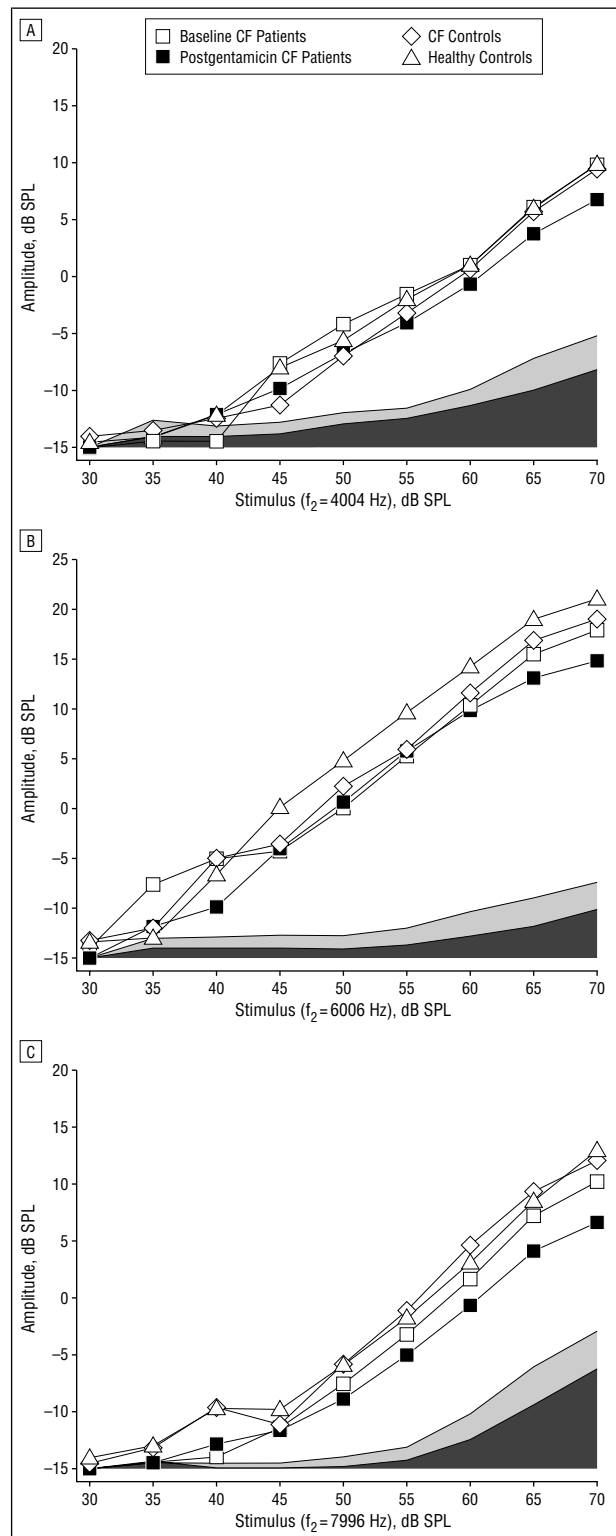


Figure 3. The baseline input-output (I/O) functions at 4004, 6006, and 7996 Hz for the 3 tested groups and the posttreatment recordings for the CF-gentamicin group. The mean values of I/O functions are A, $f_2 = 4004 \text{ Hz}$; B, $f_2 = 6006 \text{ Hz}$; and C, $f_2 = 7996 \text{ Hz}$. The lower shaded areas in all figures represent the mean noise floor plus 1 SD, while the upper shaded areas represent 2 SDs above the mean noise floor. SPL indicates sound pressure level; CF, cystic fibrosis.

ration of drug regimens. In our study, conventional PTA thresholds were within normal limits for patients with CF and a history of aminoglycoside intake and remained virtually unchanged following the last gentamicin exposure.

In some of the previously mentioned studies,^{15,19,21} results are not presented separately for children and adults, although it is obvious that the cumulative aminoglycoside dose and the potential ototoxicity in children can be expected to be lower. Furthermore, the number of properly designed, well-controlled studies is small. To our knowledge, only 2 studies^{17,22} used properly selected control groups (healthy subjects and patients with CF not treated with aminoglycoside), while in 3 other studies only healthy subjects served as a control group.^{18,20,21} Unfortunately, the criteria for defining hearing loss were not presented clearly in any of these studies.

Several investigators have used high-frequency audiometry for early detection of hearing loss.^{15,17,19,22,23} In these studies the incidence of cochleotoxic damage is the highest reported. While high-frequency audiometry is a sensitive method for early detection of ototoxicity, it is not easily applicable to children. It requires cooperation from the young patient, which cannot always be counted on. Lack of patient concentration due to poor general condition also affects audiometric results.²⁴ In addition, the procedure must be optimally carried out in a sound-treated environment and requires a sound of moderate to high intensity to elicit an observable response, even

from children with normal auditory function. The test is relatively time-consuming, and learning effects may partially obscure the detection of hearing loss.

With improved survival in CF, quality of life issues are becoming of paramount importance. Detection of hearing loss at a young age is essential when education, social integration, and personality development are at a critical stage. Typically, once damage has occurred, recovery of the cochlea cannot be expected. Along with primary prevention, early detection of hearing loss is important for providing management options. The pediatrician might have the option of adjusting the therapy to a potentially less ototoxic regimen such as antipseudomonal penicillins or third-generation cephalosporins. Likewise, early indications of a threshold shift would be useful for planning audiologic management and counseling.

Evoked OAEs measurement is a recent noninvasive method of objective cochlear investigation that is especially helpful in children. Evoked OAEs can be reliably measured from nearly all human ears with normal cochlear and middle ear function.¹⁰ It is now well established that OAEs measures are more sensitive to inner ear dysfunction than conventional PTA or auditory brainstem responses.^{7,12,25} In our study, both TE and DP OAEs were significantly affected at the higher frequencies following recent gentamicin exposure. Decreased emissions in the presence of normal behavioral hearing may indicate an underlying pathologic condition, which, if allowed to continue, might result in a clinically significant hearing loss.

The high sensitivity of DP OAEs in early identification of subtle inner ear dysfunction has also been emphasized in 2 reports on aminoglycoside used to treat patients with CF.^{21,22} However, the outcome measures used were quite different. In a study by Katbamma et al,²² a significant suppression of DP OAEs was found in 13 tobramycin-treated children compared with children with CF not treated with drugs and healthy children of similar age, suggesting that enhanced contralateral suppression may be the first sign of developing ototoxicity. In the Mulheran and Degg study,²¹ a significant elevation of the stimulus level required to generate a $2f_1-f_2$ DP OAE of 10 dB SPL or lower at 4000 Hz was found in 15 gentamicin-treated children with CF compared with normal children, suggesting that this elevation may represent one of the earliest changes in outer hair cell function caused by gentamicin.

To our knowledge, this is the first study investigating the sensitivity of both TE and DP OAEs in the early

Table 2. Effect of Aminoglycoside Therapy on Distortion-Product Otoacoustic Emissions Amplitude*

Frequency (f_2), Hz	Pretreatment Amplitude, dB SPL (n = 24 Ears)	Posttreatment Amplitude, dB SPL (n = 24 Ears)	t	P	r_{pb}
1001	4.31 (5.98)	4.98 (6.61)	-0.412	.68	...
1257	8.04 (6.25)	7.40 (8.44)	0.481	.64	...
1587	9.08 (5.44)	9.39 (6.08)	-0.309	.76	...
2002	7.00 (4.03)	6.85 (6.37)	0.134	.89	...
2515	6.58 (3.72)	5.80 (6.18)	0.727	.48	...
3174	4.97 (2.59)	2.30 (5.25)	2.418	.02	0.45
4004	10.53 (4.66)	5.35 (6.75)	3.282	.003	0.56
5042	17.68 (5.47)	10.80 (9.54)	3.410	.002	0.58
6348	11.50 (5.02)	6.53 (7.17)	3.035	.006	0.53

*Unless otherwise indicated, data are mean (SD). SPL indicates sound pressure level; t, paired t test; P, 2-tailed P value; r_{pb} , point biserial correlation coefficient¹³; and ellipses, not applicable. *df* = 23.

Table 3. Effect of Aminoglycoside Therapy on Input/Output Function Dynamic Range and Detection Threshold*

Parameter	Frequency (f_2), Hz	Pretreatment (n = 24 Ears)	Posttreatment (n = 24 Ears)	t	P	r_{pb}
Dynamic range	4004	9.84 (3.86)	6.74 (3.93)	3.384	<.001	0.57
	6006	17.91 (5.99)	14.83 (6.62)	2.367	.03	0.44
	7996	10.22 (6.37)	6.70 (6.67)	2.367	.03	0.44
Detection threshold	4004	38.10 (4.01)	42.58 (6.97)	-2.485	.02	0.46
	6006	35.00 (4.66)	37.50 (4.66)	-2.398	.03	0.45
	7996	39.77 (9.49)	44.92 (11.22)	-2.310	.03	0.43

*Unless otherwise indicated, data are mean (SD) dB. t indicates paired t test; P, 2-tailed P value; and r_{pb} , point biserial correlation coefficient.¹³ *df* = 23.

detection of gentamicin-induced cochleotoxicity in children with CF. Tests for DP OAEs seemed to be more frequency sensitive than those for TE OAEs for determining minor cochlear dysfunction. This difference may arise from different generating mechanisms within the cochlea and/or different propagation mechanisms from the inner to external ear. For monitoring purposes, DP OAEs would also seem preferable to TE OAEs because they are known to have a more extensive range regarding hearing loss and can be measured over a broader frequency range with more sensitive frequency-specific responses.⁵

Our findings suggest that evoked OAEs are a sensitive and a reliable indicator of subtle inner ear dysfunction. Their recording is easy for both technician and patient, does not require a sound-treated environment, and can be easily performed at the bedside with portable equipment. We believe that OAEs measurement should be routinely used in monitoring to prevent permanent damage, not only in the clinical evaluation of auditory function, but also for regular monitoring of cochlear function in the presence of potentially toxic factors such as aminoglycosides.

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