Factors Affecting Sensitivity of Distortion-Product Otoacoustic Emissions to Ototoxic Hearing Loss

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Objectives: **(1) To determine the ototoxicity detection rate (sensitivity) for distortion-product otoacoustic emissions (DPOAEs) testing in adults who received ototoxic medications and experienced pure-tone threshold changes during the course of treatment; (2) to determine the extent to which DPOAE sensitivity to ototoxicity depends on the type of drug administered (platinum or antibiotic), magnitude of ototoxic threshold shifts, pre-exposure pure-tone threshold, and DPOAE data; and (3) to build a model to predict DPOAE sensitivity.**

Design: **DPOAE and audiometric data were obtained as part of a prospective Veterans Affairs study investigating methods of ototoxicity monitoring. Data were analyzed from 90 ears of 53 subjects receiving ototoxic medications and showing significant hearing changes in at least one ear. Pure-tone threshold data were obtained at frequencies from 0.5 to 20 kHz, using 1/6-octave precision near the upper frequency limit of hearing. DPOAE data are reported for f_2's from 0.8 to 8.0 kHz in 1/6-octave increments using primary levels (L_1/L_2) of 65/59 dB SPL and a primary frequency ratio (f_2/f_1) of 1.2. Test results were evaluated at various times during drug treatment to determine whether DPOAE level changes were associated with behavioral hearing changes. Univariate and multivariate analysis techniques were used to determine factors that affected DPOAE sensitivity to ototoxic damage.**

Results: **Of the 90 ears examined, 82 (91%) had DPOAEs that could be monitored for changes. Sixty-four of these 82 ears (78%) had DPOAEs that were reduced or absent following drug treatment. DPOAE sensitivity to ototoxicity was unrelated to the type of ototoxic drug administered. Rather, DPOAE sensitivity depended on the magnitude of postexposure hearing changes and on variables related to pre-exposure audiogram and DPOAE measurements. Behavioral hearing changes not detected by DPOAEs were small on average (<7 dB). DPOAE sensitivity was reduced in ears with poorer pre-exposure hearing, and in ears with measurable DPOAE frequencies limited to f_2's below 2.5 kHz or more than one octave from the frequency region where hearing change occurred. Results of logistic regression modeling showed that DPOAEs present at f_2's greater than 2.5 kHz were associated with the eventual success of ototoxicity monitoring with DPOAEs. However, independent variables examined could not explain differences in the relative timing of behavioral and DPOAE changes. A roughly equivalent proportion of ears experienced DPOAE changes before, during, or after behavioral hearing changes.**

Conclusions: **DPOAEs are a useful screening tool for ototoxicity in adults with pre-exposure hearing loss, but are less sensitive compared with a behavioral test method that targets thresholds near the upper limit of a subject's audible frequency range. Ears successfully monitored for ototoxicity with DPOAEs are those with better pre-exposure hearing, greater postexposure hearing changes, and baseline DPOAEs near the highest behavioral test frequencies and present at high f_2's. Results suggest that successful monitoring of ototoxicity with DPOAEs may be predicted clinically by assessing the measurable DPOAE f_2 frequency range and its relation to the highest behavioral test frequencies.**

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INTRODUCTION

Life-threatening medical conditions may require treatment with highly ototoxic agents, and the risk of hearing loss may be unavoidable. In many cases, however, alternative drugs, reduced dosages or altered treatment regimens are options if ototoxicity is detected early in the treatment period. There are over 130 medicinal and chemical agents with potential for damaging the cochlear and/or vestibular end organs (Seligmann, et al., 1996). Platinum-based chemotherapy agents and aminoglycoside antibiotics are commonly prescribed drugs known to be cochleotoxic. Because of their wide usage, such ototoxic drugs have a large impact on the occurrence of hearing loss.

Cisplatin and carboplatin are antineoplastic chemotherapeutic agents used to treat a variety of tumors in both adults and children. High-dose carboplatin therapy is also used with stem cell/bone marrow transplants. Cisplatin causes ototoxicity in

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a large percentage of patients treated. Schweitzer (1993) calculated that the incidence of cisplatin-induced hearing loss averaged across a large number of studies was 62% (the range was 11%–97%). The incidence of carboplatin-induced hearing loss is comparatively lower, ranging from 19% (Kennedy, et al., 1990) to 82% (Parsons, et al., 1998).

The most common clinical application of aminoglycosides is in the treatment of serious infections caused by aerobic gram-negative bacteria. The incidence of aminoglycoside-induced hearing change reported in the literature ranges from 0.6% to 30% (Brummett & Fox, 1989; Lesar, 1993). Compared with aminoglycosides, platinum-based drugs are more cochleotoxic.

Predicting which patients will experience ototoxic hearing loss is a clinical challenge. The risk for developing hearing loss from ototoxic drugs is generally correlated with dosage. However, this relationship is highly variable (Blakley, et al., 1994; de Jongh, et al., 2003; Moore, et al., 1984; Waters, et al., 1991). Individual susceptibility to ototoxic hearing loss is influenced by multiple biochemical, physiologic, and genetic factors (Fischel-Ghodsian, et al., 1993; Forge & Schacht, 2000).

Not only is ototoxicity difficult to predict, but early signs are often missed if hearing is not directly monitored. Ototoxic damage typically begins near the high-frequency coding cochlear base and progresses toward the apex of the cochlea (Brummett, 1980; Komune, et al., 1981; Konishi, et al., 1983; Nakai, et al., 1982; Schweitzer, et al., 1984). Communication problems can be an indication that hearing changes have begun to impact the frequency range important for speech understanding. Unfortunately, patients tend not to complain of hearing difficulties until a communication problem becomes significant.

Early identification of ototoxic damage through prospective monitoring allows for the consideration of treatment modifications to minimize or prevent the progression of permanent hearing loss. Serial testing of pure-tone thresholds at conventional audiometric test frequencies from 0.25 to 8.0 kHz in one octave steps is the most common method for ototoxicity monitoring. Numerous studies have shown that use of extended-high frequency threshold testing from 9 to 20 kHz improves the sensitivity of monitoring techniques (Dreschler, et al., 1989; Fausti, et al., 1984, 1992, 1993, 1994; Ress, et al., 1999; Tange, et al., 1985; van der Hulst, et al., 1988).

A related strategy to improve the sensitivity of behavioral monitoring techniques involves the determination of an operationally-defined high-frequency hearing limit followed by pure-tone threshold testing (usually with 1/6-octave precision) within a one-octave range up to this limit. Thus, the frequency range targeted for monitoring varies across patients, depending on their pre-exposure hearing ability. Studies have shown that in about 90% of ears, cisplatin, carboplatin and ototoxic antibiotic-induced hearing changes presented first within this one-octave range of frequencies called the sensitive range for ototoxicity or SRO (Fausti, et al., 1999, 2003; Vaughan, et al., 2002).

Another proposed strategy to improve the sensitivity of ototoxicity monitoring includes using otoacoustic emission (OAE) testing. Pathologies that warrant treatment with ototoxic drugs and/or radiation, as well as the treatments themselves, can cause fatigue, potentially reducing the accuracy of behavioral data. OAEs have been proposed as an alternative for behavioral measures of auditory function, which may be of questionable reliability in very ill patients. OAEs have been used widely for ototoxicity monitoring in pediatric populations receiving aminoglycoside antibiotics in which OAE changes tend to occur before conventional frequency pure-tone threshold changes (Katbamna, et al., 1999; Mulheran & Degg, 1997; Stavroulaki, et al., 2002). Objective measures that do not require cooperation or concentration are thought to be important tools for the early detection and monitoring of ototoxic damage in patients who are too ill or young to provide adequate behavioral data or endure long test protocols. However, it is still not clear to what extent clinical decisions about therapeutic treatment should be based on OAE changes.

Distortion-product (DP) OAE testing provides a noninvasive, objective measure of cochlear function. A DPOAE is an acoustic response generated by the outer hair cells within the cochlea and reverse-transmitted through the middle ear into the ear canal. The response is initiated in the overlapping region of the basilar membrane's response to two stimulating tones, f_1 and f_2 (where $f_1 < f_2$), somewhat nearer to the f_2 tonotopic place. A second component arises near the basilar membrane place that codes the distortion-product frequency ($2f_1$-f_2) (Kim, 1980; Shera & Guinan, 1999). Clinical DPOAEs are comprised of these two sources combined within the ear canal. Results from animal models of ototoxicity (Estrem, et al., 1981; Meech, et al., 1998; Tange, 1984; Tsukasaki, et al., 2000) and human temporal bone studies (Hinojosa, et al., 1995, 2001; Hoistad, et al., 1998) demonstrate that ototoxic agents primarily damage the outer hair cells and the stria vascularis, which provides the electrical drive to the outer hair cells. These ototoxic-induced changes to the outer hair cell system, in turn alter OAE responses (reviewed in Campbell & Durrant, 1993 and Whitehead, et al., 1996).

Numerous studies in young subjects have shown that changes in DPOAE responses often precede behavioral threshold shifts at corresponding frequencies, and that in some cases, corresponding behavioral threshold shifts never occur (aminoglycosides: Katbamna, et al., 1999; Littman, et al., 1998; Mulheran & Degg, 1997; Ozturan & Lam, 1996; Stavroulaki, et al., 2002; cisplatin: Stavroulaki, et al., 2001). A frequently studied population for the assessment of DPOAE sensitivity in ototoxic-induced hearing loss is children and young adults with cystic fibrosis who receive the aminoglycoside antibiotics gentamicin and/or tobramycin on a routine basis.

Mulheran and Degg (1997) assessed DPOAE sensitivity through the generation of input/output (I/O) growth functions and detection of emission thresholds in a retrospective cross-sectional study of adolescent cystic fibrosis patients who received frequent gentamicin treatments. Pure-tone thresholds were measured from 0.25 to 12 kHz and DPOAE I/O growth functions were measured at the f_2 frequencies of 2, 4, and 6 kHz in 14 subjects receiving gentamicin and in 36 healthy volunteers. All subjects were otologically normal including audiometric thresholds (0.25–8 kHz ≤10 dB HL). Using Student's two-tailed t tests, the authors reported no significant pure-tone audiometric threshold differences between the treatment and control groups. However, DPOAE threshold was significantly elevated at 4 kHz in the gentamicin treatment group when compared with the controls. This study was unable to determine if the DPOAE threshold difference detected at 4 kHz between groups was an early indicator of ototoxic damage or an expression of cystic fibrosis itself.

A prospective study was conducted by Stavroulaki et al. (2002) which compared the sensitivity of conventional pure-tone audiometry (0.25–8 kHz) with DPOAE testing ($f_2$1.0–6.4 kHz) in the detection of gentamicin-induced ototoxicity in children with cystic fibrosis. Pure-tone thresholds and DPOAEs recorded pretreatment were compared with posttreatment recordings. DPOAEs were collected in the form of DP-grams, in which DPOAE amplitudes are plotted for a range of f_2 frequencies presented at a constant level (L_2). Equal-level primaries were used with $L_1 = L_2 = 70$ dB SPL. Clinically significant hearing changes were determined based on criteria from the American Speech-Language-Hearing Association (ASHA, 1994) which include 20 dB threshold shift at a single frequency, 10 dB shift at two adjacent frequencies, or loss of response at three adjacent frequencies. A two-tailed paired Student's t test was used to assess DPOAE amplitude changes. A significant decrease in DPOAE amplitudes was noted in the children receiving gentamicin when compared with drug-free cystic fibrosis patients and healthy children of a similar age. The observed DPOAE amplitude changes occurred at the four highest f_2 frequencies tested, 3.2, 4, 5, and 6.4 kHz. Changes in DPOAE amplitudes were attributed to gentamicin administration and were noted in the absence of pure-tone threshold changes. The authors concluded that DPOAEs were more sensitive to the early effects of aminoglycoside induced ototoxicity when compared with audiometry. However, behavioral threshold testing was limited to conventional audiometric frequencies so changes above 8 kHz were not assessed.

Katbamna et al. (1999) investigated DPOAE amplitudes, latency, and I/O growth functions in adolescent and young adult cystic fibrosis patients with documented exposure to tobramycin and compared them to control subjects with no history of ototoxic drug exposure. DP-grams were constructed for f_2 frequencies swept from 1.6 to 8 kHz with the primary tone levels L_1/L_2 set to 65/50 dB SPL. DPOAE latency measurements were obtained at the f_2 frequencies 2, 2.8, 4, 5.6, and 8 kHz and growth functions were obtained at the f_2 frequencies 4.3 and 8.5 kHz. In addition to conventional pure-tone audiometry, the authors included extended-high frequency audiometry up to 20 kHz. Analysis of variance was used to assess differences in both pure-tone audiometry and in DPOAE measurements. Katbamna et al. (1999) found no significant group differences in DPOAE amplitude or pure-tone thresholds in subjects receiving tobramycin and their drug-free counterparts. However, DPOAE I/O growth function and latency differences were noted in the absence of corresponding audiometric differences. Patients who had a history of tobramycin exposure showed significantly elevated I/O detection thresholds and longer latencies at all measured frequencies compared with their drug-free counterparts. DPOAE threshold differences in the absence of audiometric differences at extended-high frequencies were thought to reflect subclinical physiologic effects of aminoglycoside ototoxicity.

Stavroulaki et al. (2001) investigated the role of DPOAEs in the detection of cisplatin-induced ototoxicity in 12 children. This prospective study compared pretreatment measures of DPOAE amplitudes, collected in the form of DP-grams, (f_2 = 0.8–6.3 kHz with equal-level primaries $L_1 = L_2 =$ 70 dB SPL), DPOAE I/O growth functions (f_2 = 4, 6, and 8 kHz in 10 dB steps from 35 to 70 dB SPL) and conventional audiometry (0.25–8 kHz) to recordings obtained after a single dose of cisplatin. ASHA (1994) criteria were used to determine significant pure-tone threshold changes and a two-tailed,

paired Student's *t* test was used to determine significant DPOAE changes. Posttreatment measures documented mild to moderate hearing loss from 6 to 8 kHz in 50% of the children. The mean difference in average pure-tone thresholds measured before and after infusion was found to be significant from 4 to 8 kHz. All patients demonstrated a statistically higher DPOAE detection threshold after infusion at f_2 frequencies 4, 6, and 8 kHz. The mean difference in DPOAE amplitudes recorded before and after drug infusion was statistically significant at f_2 frequencies ≥3 kHz. The presence of such DPOAE amplitude changes at 3 kHz in the absence of hearing changes suggest OAEs may be used to monitor cochlear damage that impacts hearing at higher frequencies and may foretell further damage should cisplatin infusion continue.

Few studies have examined DPOAE sensitivity to ototoxicity in adult subjects with pre-exposure hearing loss. Ress et al. (1999) performed a prospective study comparing the relative sensitivity of DPOAEs, conventional audiometry (≤8 kHz), and extended-high frequency (>8 kHz) audiometry to ototoxic damage in 33 adults receiving cisplatin chemotherapy. Mean age of subjects was 62 years (range, 42–80 years) with average hearing levels at 6 and 8 kHz >40 dB HL. Preinfusion DP-grams were recorded for geometric mean frequencies from 0.8 to 8 kHz and compared with postinfusion recordings. Equal-level DPOAE primaries were set to 65 or 75 dB SPL. At baseline with 75 dB SPL primaries, approximately 80% of ears exhibited measurable DPOAEs from 1 to 6 kHz and 50% of ears exhibited measurable DPOAEs above 6 kHz. DPOAEs obtained using 65 dB SPL primaries were measurable in even fewer ears at baseline, and subsequently were not evaluated. Changes in pure-tone thresholds were determined using ASHA (1994) criteria. DPOAE changes were determined clinically with a decrease of >5 dB at two or more frequencies and statistically through repeated-measures analysis of variance. Following drug exposure, average pure-tone thresholds changed in the frequency range from 2 to 14 kHz, whereas average DPOAE amplitudes were reduced for frequencies >2 kHz and absent at all frequencies >5 kHz. The proportion of ears showing ototoxic change was similar for DPOAE (75%) and behavioral threshold testing in the extended-high frequency range (74%). Moreover, the sensitivity of both methods was greater compared with conventional audiometry (65%). More ears were able to be monitored using high-level DPOAE techniques (82%) than extended-high frequency audiometry (54%) because some subjects lacked the ability to hear above 8 kHz.

Taken together, results in children with good pre-exposure hearing and in adults with pre-existing hearing loss suggest that DPOAE testing is at least as effective as behavioral testing for ototoxicity monitoring. However, it remains unclear how DPOAE sensitivity compares with a behavioral test method that targets thresholds near the upper limit of a subject's audible frequency range.

Previous reports have examined DPOAE responses in clinical patients exposed to ototoxic agents as part of therapeutic treatment, yet no studies have examined factors that influenced the success or failure of DPOAEs to predict ototoxic hearing changes. It is likely that pre-exposure (i.e., baseline) hearing affects DPOAE sensitivity in an adult population in which normal pre-exposure hearing cannot be assumed. In particular, successful monitoring of ototoxicity with DPOAEs might depend on the ability to record DPOAEs near each individual's high-frequency hearing limit where initial hearing changes present. It is important to recognize this limit could be within the extended-high frequency range for some individuals and within the conventional frequency range for others. It is also likely that the magnitude of postexposure hearing loss affects DPOAE sensitivity to ototoxic damage. Data concerning these potential relationships are lacking. Consequently, the clinical significance of DPOAE changes (or of the lack of DPOAE changes) observed following ototoxic drug exposure is unknown.

The present study involves DPOAE and pure-tone threshold data obtained as part of a large, prospective study investigating methods of ototoxicity monitoring in patients receiving cisplatin, carboplatin, or ototoxic antibiotics for the treatment of cancer or infectious diseases. DPOAE testing was compared with a behavioral testing method developed by Fausti et al. (1999) that monitors thresholds near each subject's high-frequency hearing limit. Objectives of this report were (1) to determine the ototoxicity detection rate (sensitivity) for DPOAE testing in adults who were receiving ototoxic medications and experienced pure-tone threshold changes during the course of treatment; (2) to determine the extent to which DPOAE sensitivity to ototoxicity depends on the type of drug administered, magnitude of ototoxic threshold shifts, and pre-exposure pure-tone threshold and DPOAE data; and (3) to build a model to predict DPOAE sensitivity.

MATERIALS AND METHODS

Subjects

Subjects were adult inpatients and outpatients recruited from Veterans Affairs Medical Centers located in Portland, Oregon, Nashville, Tennessee, and West Los Angeles, California. Behavioral re-

sults have been reported previously for many of these subjects (Fausti, et al., 1999, 2003). The present report describes data obtained in 53 subjects with complete data sets that provided baseline measurements, and confirmed behavioral threshold shifts in at least one ear. Fifty-one men and two women met inclusion criteria for the study with a mean age of 59 years (range, 46–82 years of age).

Inclusion criteria for the study were (1) received at least one chemotherapeutic treatment of cisplatin or carboplatin or more than three days of specified ototoxic antibiotic medications, (2) normal middle-ear function based on 226 Hz tympanometry, (3) no history of retrocochlear or Meniere's disease, (4) able to respond reliably to behavioral pure-tone audiometry, and (5) evidence of ototoxic shifts in hearing sensitivity based on ASHA (1994) criteria (described below). Subjects served as their own control for hearing and OAE change, which was relative to responses obtained during a baseline (usually pre-exposure) evaluation. All subjects were consented to participate in the study following the guidelines of each medical center's Institutional Review Board and were compensated for their time.

Equipment and Calibration

Behavioral audiometry • Pure-tone thresholds were established from 0.5 to 20 kHz using a Virtual Corporation, Model 320 (V320) audiometer. TDH-50P earphones in MX-41/AR cushions were used for testing 0.5 and 1 kHz thresholds. Koss Pro/4X Plus earphones, modified to improve signal-to-noise ratio for high frequency testing (2–20 kHz) as described in Fausti et al. (1990), were used for testing frequencies from 2 to 20 kHz. Reliability, validity, and equipment limits of 115 dB SPL for frequencies 2 to 20 kHz for threshold responses using the Virtual V320 audiometer paired with modified Koss Pro/4X Plus earphones have been documented previously (Fausti, et al., 1990).

Calibration of the Virtual V320 audiometer was conducted twice each month. TDH-50P earphones were calibrated according to ANSI S3.6-1989 (1989) and IEC 318 specifications. The earphone was coupled to a Bruel & Kjaer (B&K) 4153 artificial ear and the acoustic output was measured by a B&K 4134 ½ inch condenser microphone and read on a B&K 2231 sound level meter. KOSS Pro/4X Plus earphones were calibrated on a 6 cm^3 flat-plate coupler with a B&K 4134 ½ inch condenser microphone in the center of the cavity (as described in Fausti, et al., 1979).

Distortion-product otoacoustic emissions • DPOAEs were collected with an Intelligent Hearing Systems SmartDPOAE system. Primary tones (f_1, f_2) were generated by separate (Etymotic Research) ER-2 tubephones. The ER-2s were coupled to the ER-10B+ microphone probe assembly with silicone tubing (278 mm). ER7-14C probe tube extensions were inserted into the silicone tubing and through the steel sleeves of the probe assembly with the aim of minimizing distortion and extending the measurement frequency range. The probe assembly was sealed with a foam tip in the subject's external ear canal. The sound pressure in the ear canal was measured by the ER-10B+ low noise microphone, amplified (+20 dB gain), and sampled at a rate of 32 kHz. The FFT binwidth was 7.8 Hz.

Acoustic calibration of the SmartOAE system was performed annually using the calibration program contained within the system. The procedure involved coupling the ER-10B+ probe assembly to a B&K 4157 ear simulator that was connected via a B&K 2669 preamplifying cable to a B&K 2231 sound level meter. Pure-tones were presented at octave intervals from 0.125 to 16 kHz, at a desired level of 70 dB SPL. Voltages applied to the ER-2s were adjusted until the output level read by the sound level meter matched the desired output level of 70 dB SPL. Levels of 70 dB SPL were typically able to be achieved even at the highest frequencies calibrated with minor adjustments. However, high primary frequencies produced high levels of system distortion. (See Procedures section for a more detailed discussion of system distortion measurements.)

Initially, outputs from each stimulus channel were calibrated in each subject's ear canal. For this individualized "in-the-ear-calibration" technique, the output sampled by the ER-10B+ microphone is used to adjust the voltage across the terminals of the source transducers. This, in turn, sets the SPL of f_1 and f_2 to desired values. The approach works well for the lower primary frequencies and for smaller ear canal volumes. Above about 3 kHz and especially in larger ear canal volumes, interactions of incident and reflected waves produce pressure nodes within the ear canal because of standing waves. These pressure nodes may result in calibration errors (Siegel, 1994). In addition, their presence (even when the SPL at the lateral surface of the tympanic membrane is accurate) may lead to an increase in the driving-point voltage required to achieve the desired SPL at the plane of the microphone. Evaluation of ear-canal recordings indicated that increases in the driving-point voltage related to in-the-ear calibration increased distortion artifacts at $2f_1$-f_2 that were not attributable to biological DPOAE responses.

In an attempt to improve extended high-frequency DPOAE data above 8 kHz, the in-the-ear calibration procedure was abandoned during the

course of the study so that we ultimately used only the coupler calibration method described above. Every effort was made to maintain consistent probe placement across serial measurements. However it is understood that there is some uncertainty regarding the stimulus levels reaching the tympanic membrane using this approach. Although calibration procedures changed during the study (use and disuse of in-the-ear calibration), the particular calibration strategy used for each subject was maintained throughout testing. In other words, if a patient was initially tested with in-the-ear calibration procedures, then in-the-ear calibration procedures were used for the remainder of that patient's test sessions. Responses at frequencies >8 kHz were often unable to be distinguished from the system distortion even when in-the-ear calibration was not completed. Therefore, data collected for frequencies >8 kHz were not analyzed in this report. At the reported stimulus levels (L_1 = 65 dB SPL) and frequencies (<8 kHz) one would expect in-the-ear calibration methods to yield slightly different mean DPOAE amplitudes compared with calibration strategies that apply a constant voltage across frequencies (a variant of the coupler method) within the same subject (Whitehead, et al., 1995). However, since calibration procedure (in-the-ear versus coupler) was maintained for repeated measures within each subject, the modification to our calibration procedures was not expected to have an effect on the reported results.

Calibration procedures using SPL measurements at the plane of the microphone are known to produce calibration errors, particularly at the higher frequencies (Siegel, 1994, 2002). Calibration procedures that measure intensity or power of the stimulus rather than pressure may reduce the effects of standing waves (Neely & Gorga, 1998) and thus decrease the overall variability in OAE measurements. Calibration strategies in small cavities should be thoughtfully considered when measuring OAEs and certainly warrant further investigation.

Procedures

Baseline tests occurred within 24 hours of the first drug treatment for platinum-based drugs and within 72 hours of the first treatment for ototoxic antibiotics. A retest was performed within 24 hours of baseline, if possible, to validate intersession reliability. Monitor evaluations were attempted within 24 hours of every platinum-based treatment and every 2 to 3 days during ototoxic antibiotic treatment. Immediate posttreatment, one, three, and 6-month follow-up evaluations were scheduled as subjects' health and schedules permitted. All data were collected with subjects seated comfortably in a recliner located in a standard, double-walled, sound treated booth. Otoscopy, tympanometry, pure-tone audiometry, and DPOAE testing were performed at each test session.

Behavioral monitoring • Pure-tone air conduction thresholds were obtained using a modified Hughson-Westlake procedure (Carhart & Jerger, 1959) with pulsed tones. Frequencies tested were standard audiometric frequencies from 0.5 to 8 kHz in one-octave step sizes, and the interoctave frequencies 3 and 6 kHz. In addition, thresholds were tested in 1/6-octave steps from 9 to 20 kHz. If a behavioral response was not present at equipment limits (115 dB SPL 2–20 kHz), then the audiometric threshold was arbitrarily set to 120 dB SPL. Baseline testing involved the determination of an individualized, SRO defined as the uppermost frequency at which threshold is 100 dB SPL or less and the six consecutive lower frequencies in 1/6-octave steps (Fausti, et al., 1999). Therefore, depending on the patient's hearing thresholds, testing in 1/6-octave intervals could extend below 8 kHz to as low as 2 kHz. For subsequent test sessions, pure-tone thresholds were obtained at standard frequency increments up to 20 kHz and with 1/6-octave precision for frequencies within the subject's SRO, as defined at baseline.

Criteria for significant changes in behavioral thresholds • Criteria for significant changes in behavioral hearing sensitivity were defined according to ASHA published "Guidelines for the Audiologic Management of Individuals Treated with Cochleotoxic Drug Therapy" (ASHA, 1994). These criteria include (a) ≥20 dB change at any one test frequency; or (b) ≥10 dB changes at any two consecutive test frequencies; or (c) loss of response at three consecutive frequencies where responses were previously obtained. All changes were confirmed by retesting the audiometric thresholds, consistent with these guidelines.

DPOAE monitoring • DPOAEs were recorded for primary frequency pairs with f_2/f_1 set to 1.2 and f_2 varied from 0.8 to 16 kHz in 1/6-octave steps. Primary frequency sweeps were performed at each of three (fixed) level combinations (L_1/L_2 was 75/69, 70/64, or 65/59 in dB SPL). System distortion was estimated by examining the level of the cubic distortion product recorded in a B&K 4157 artificial ear for each of these primary frequency and level conditions. Because of high levels of system distortion at higher intensities and higher frequencies, only DPOAE measurements for L_1/L_2 = 65/59 and for f_2 frequencies from 0.8 to 8 kHz were analyzed. To be considered a valid response, DPOAE level had to exceed −10 dB SPL (a conservative estimate of the

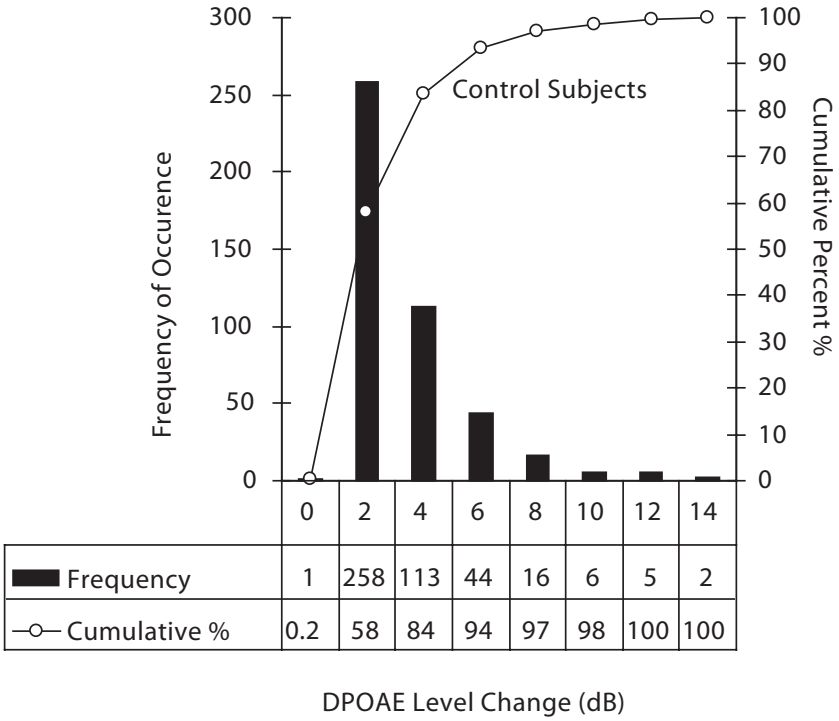

Fig. 1. Histogram plotting frequency of occurrence of DPOAE test-retest level changes (referenced to left axis) and cumulative distribution of these level changes (referenced to right axis) in control subjects not receiving ototoxic drugs.

system distortion for the stimulus conditions analyzed), and the DPOAE level had to be 6 dB greater than the noise level averaged across the three frequency bins below the $2f_1$-f_2 frequency and the three frequency bins above the $2f_1$-f_2 frequency.

Criteria for significant changes in DPOAE level • The literature pertaining to DPOAE ototoxic change criteria involves studies performed in healthy, normal-hearing subjects. Such individuals may not be representative of adult patients with hearing loss and illnesses that warrant treatment with ototoxic drugs. To determine criteria for a "clinically-significant" DPOAE change in this population, an analysis of DPOAE test-retest repeatability was performed for four control subjects using the DPOAE system parameters employed in the present study. These subjects were inpatients at the Portland VA Medical Center who were not receiving ototoxic medications, had mild to moderate, high-frequency hearing loss, and no indications of retrocochlear or middle ear pathologies.

The eight ears of the four control subjects were tested at least four times over a period of 2 to 7 months yielding 445 possible test-retest difference calculations. DPOAEs were collected in the same manner as for the subjects receiving ototoxic drugs. Figure 1 illustrates DPOAE test-retest level differences for these control subjects with results collapsed across frequencies from 0.8 to 8 kHz. The x axis bins represent absolute DPOAE test-retest level differences in 2 dB increments. Data are presented in the form of a histogram, with y values (referenced to the left y axis) indicative of the number of times each test-retest difference was observed. There was one occurrence out of 445 test-retest conditions in which the absolute level was exactly the same between two tests accounting for 0.2% of the total occurrences. A total of 258 test-retest differences fell between 0 and 2 dB and 113 test-retest differences fell between 2 and 4 dB.

The data in Figure 1 are also presented in the form of a cumulative distribution, with y values referenced to the right y axis. In total, test-retest differences from 0 to 4 dB accounted for 84% of the total variability between test sessions (i.e., [1 + 258 + 113]/445 = 84%). Inclusion of the 6 dB bin increased the total cumulative percent from 84% (0–4 dB bin) to 94% (0–6 dB). In other words, 6 dB is the 94% point on the test-retest cumulative distribution. These results suggest that a level change of about 6 dB or greater at a single frequency will yield a false positive rate of about 6%, consistent with DPOAE test-retest differences reported previously for healthy young subjects (e.g., Beattie, et al., 2003; Franklin, et al., 1992; Roede, et al., 1993).

A 6 dB shift in DPOAE level is large relative to the DPOAE dynamic range, and DPOAE level changes in subjects not receiving ototoxic drugs (in whom these changes are assumed to be false positive responses) tend not to occur at adjacent frequencies, at least for 1/2-octave (i.e., comparatively larger) f_2 step sizes (Dreisbach, et al., 2006). Therefore, it was hypothesized that a DPOAE level shift 4 dB or greater at adjacent f_2 frequencies might allow for

TABLE 1. Hearing changes by drug

	Hearing Change (Subjects)		SRO Change (Ears)	
	Unilateral	Bilateral	Within SRO	Outside SRO
Cisplatin	7 (19.4%)	29 (80.6%)	63 (97%)	2 (3%)
Carboplatin	5 (50%)	5 (50%)	12 (80%)	3 (20%)
Ototoxic antibiotics	4 (57.1%)	3 (42.9%)	7 (70%)	3 (30%)
Total	16 (30.2%)	37 (69.8%)	82 (91.1%)	8 (8.9%)

increased test sensitivity while maintaining an acceptable false positive rate. Of the 409 potential occurrences for adjacent frequency shifts in the eight control ears tested, DPOAE amplitude shifts ≥4 dB were only observed 5% (21/409) of the time. Thus, DPOAE change criteria in this study were defined as a ≥4 dB level reduction or loss of response (i.e., a previously valid DPOAE is reduced in level to below −10 dB SPL) at two or more adjacent test frequencies, with an expected false positive rate of about 5%.

When evaluating the sensitivity of DPOAEs to ototoxic hearing changes, DPOAE changes were not required to occur at the same test frequency or on the same test date as the initial behavioral change. Rather, DPOAE changes were taken at the first test session showing a significant DPOAE level shift using the criteria described above and it was noted whether the change occurred before, at the same time or after behavioral changes. Factors thought to affect DPOAE sensitivity are considered first for DPOAE changes observed at any point during treatment. If found to be significant by univariate analyses, factors were further evaluated to determine whether they affected the timing of DPOAE changes relative to initial changes in hearing.

Statistical Analysis

Data were collected in the form of categorical and continuous variables. Descriptive statistics were used throughout. Categorical data was analyzed using the Chi-square distribution. Continuous data were analyzed using one-way analysis of variance (ANOVA), and post hoc analysis, when necessary, were adjusted using Bonferroni applications. Nonparametric tests included the Mann–Whitney U. Calculated p values were considered statistically significant at or below an alpha value of 0.05. Independent variables with a p value ≤0.25 were considered in a multiple logistic regression model to determine the best predictors of DPOAE sensitivity. Backwards step-wise regression was used to determine the final model including only variables with significance at a 0.05 level.

RESULTS

Ototoxic Hearing Changes

Of the 53 subjects included, 36 received the ototoxic agent cisplatin, 10 received carboplatin, and 7 received the aminoglycoside antibiotics amikacin or gentamicin, or the glycopeptide antibiotic vancomycin. Sixteen subjects experienced hearing changes in one ear and 37 experienced hearing changes in both ears, yielding 90 ears for analysis of DPOAE sensitivity. Table 1 provides the rates of occurrence of unilateral and bilateral hearing change in these subjects as a function of drug treatment. Also included in Table 1 is a breakdown of the ears with behavioral changes confined to SRO frequencies. Across treatment groups, 91% (82/90) of ears showed initial hearing changes within an octave of the highest audible frequency. Seven ears had initial hearing changes at frequencies below the SRO. One ear had ototoxic changes at two adjacent frequencies from 105 dB SPL at baseline to 115 dB SPL after treatment. Thus, these ASHA-significant hearing changes were above the SRO where, by definition, thresholds cannot exceed 100 dB SPL.

Cumulative dosages are given in Table 2 for dates corresponding to the first significant behavioral threshold change observed, and the last test obtained in each subject. Also provided in Table 2 is the duration of therapeutic treatment corresponding to the initial significant behavioral hearing change. The mean cisplatin dosage at the first sign of significant behavioral change was 343.6 mg, consistent with previous findings that rates of ototoxicity increase dramatically when the cumulative dose approximates 400 mg (Schaefer, et al., 1985) or less if thresholds are noted by extended-high-frequency audiometry (Kopelman, et al., 1988). Carboplatin-induced ototoxicity is also affiliated with high-dose therapy (Cavaletti, et al., 1998; DeLauretis, et al., 1999; Kennedy, et al., 1990). Conversely, aminoglycoside therapy is less associated with cumulative dose and more significantly associated with duration of therapy exceeding a week to 10 days (Peloquin, et al., 2004) or shorter durations if combined with another ototoxic agent (Bates, et al., 2002). In the

TABLE 2. Drug regimem

	N (Subjects)	Mean	SD	Min	Max
A. Dosage at first hearing change (mg)					
Cisplatin	36	343.6	196.2	94.0	941.0
Carboplatin	10	1624.0	625.5	420.0	3125.0
Ototoxic antibiotics	7	19370.0	9417.6	1200.0	35000.0
B. Total dosage subject received (mg)					
Cisplatin	36	527.6	234.7	192.0	1132.0
Carboplatin	10	2013.3	661.3	1180.0	3645.0
Ototoxic antibiotics	7	25160.0	12485.4	1200.0	39500.0
	N (Ears)	Mean	SD	Min	Max
C. Number of days to first change					
Cisplatin	65	61.7	59.6	1.0	290.0
Carboplatin	15	89.8	43.6	20.0	162.0
Ototoxic antibiotics	10	68.5	79.7	7.0	206.0

(A) Mean dosage at the test date corresponding to the first significant hearing change reported in subjects; (B) The total dosage received by subjects. All dosages are given in mg; (C) Number of days between first dose and first significant hearing change, reported in ears.

present analysis, ototoxic antibiotic drug therapy continued an average of 68.5 days (SD = 79.7; range 7–206 days) before significant behavioral hearing changes were noted.

Mean behavioral thresholds obtained at the baseline evaluation (dashed line) are given in Figure 2 as a function of frequency from 0.5 to 20 kHz. Threshold responses unable to be obtained at equipment limits (115 dB SPL) were arbitrarily set to 120 dB SPL for inclusion into the average. For comparison, the test date on which hearing changes were first observed (thin line) and the final test obtained for each subject (thick line) are plotted. Mean threshold shifts up to about 15 dB were found. Eighty-nine percent (80/90) of ears in this sample had thresholds above 8 kHz at baseline. The percentage of ears with pure-tone thresholds which could be measured within the intensity limits of the audiometric equipment (115 dB SPL from 2 to 20 kHz) declined as frequency increased. At baseline, approximately 50% of ears (44/90) had measurable hearing thresholds at 12.5 kHz (median) and above. This rapidly declines to 28% (25/90) at 14 kHz, 6% (5/90) at 16 kHz, and 2% (2/90) at 20 kHz. Mean thresholds at frequencies beginning around 16 kHz were near 120 dB SPL, indicating that many subjects had no responses at these higher frequencies.

Figure 3 shows an example of audiometric thresholds (circles, referenced to the right y axis) and DPOAE levels (triangles, referenced to the left y axis) recorded from a typical subject at baseline. The high-frequency hearing limit for this subject was operationally defined as 12.5 kHz, which in turn defined the SRO (the one-octave range below this limit indicated by filled circles) with frequencies tested in 1/6-octave steps (6.35, 7.13, 8, 9, 10, 11.2, 12.5 kHz). DPOAEs in this example could be measured only up to 4.4 kHz, which is not surprising

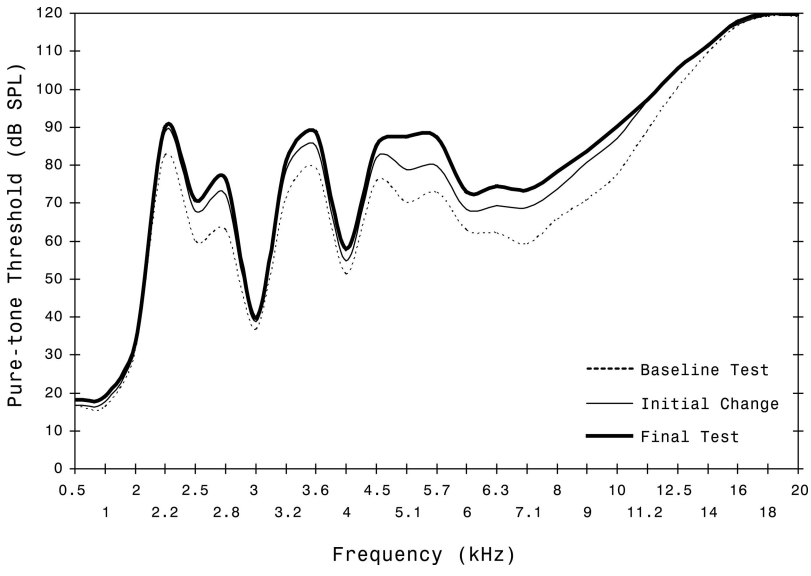

Fig. 2. Comparison of pure-tone thresholds before and after ototoxic drug exposure in ears showing significant pure-tone threshold changes. Mean thresholds in dB SPL are given for the baseline evaluation (dashed line), the test session when initial ASHA-significant hearing changes were observed (thin line), and the final test obtained for each subject (thick line). For ease in displaying results, no response was set to 120 dB SPL.

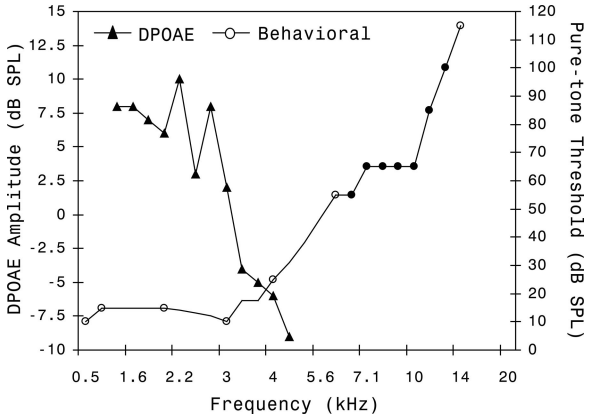

Fig. 3. Behavioral thresholds (referenced to the right axis) and DPOAE levels (referenced to the left axis) as a function of frequency in a typical subject. The filled circles represent the behavioral SRO where early hearing changes would be expected. The triangles represent the DPOAEs with valid responses that could be monitored for ototoxic changes. Notice there is no overlap between the DPOAEs and the behavioral SRO which, occurs at higher frequencies. The x axis labels are for 1/6-octave frequencies from 0.5 to 20 kHz.

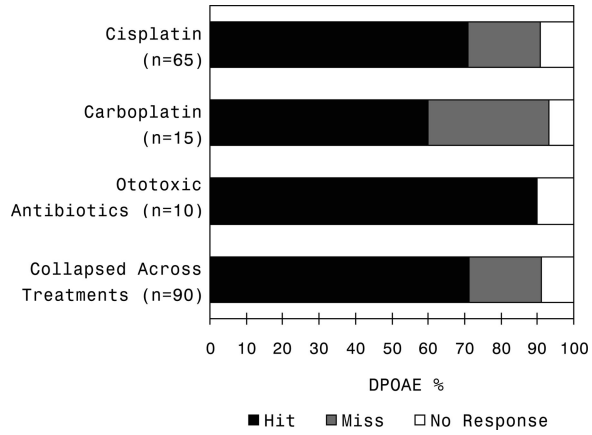

Fig. 4. Stacked bar graph showing percentage of DPOAE hits (filled bars), misses (gray bars), and no responses (open bars) as a function of drug treatment group. Also shown are data collapsed across treatment groups.

given that behavioral thresholds at 6 kHz and above were at least 55 dB SPL. As a result, DPOAEs could not be monitored at f_2's corresponding to behavioral SRO frequencies at which early threshold shifts were observed. This was a common occurrence in our subject sample because of limitations of the particular DPOAE recording system used (DPOAEs could be recorded reliably only up to 8 kHz) and because moderate DPOAE stimulus levels were used (which may not be of a sufficiently high level to evoke a DPOAE in a subject with hearing loss).

DPOAE Sensitivity

Of the 90 ears demonstrating ototoxic hearing changes using ASHA (1994) criteria given in the Methods section, 82 ears (91%) had measurable DPOAEs that could be monitored for ototoxic changes. The remaining eight ears (9%) did not have DPOAEs that could be monitored and comprise the DPOAE No Response group. Sixty-four of the 82 ears (78%) that could be monitored for DPOAE changes showed a ≥4 dB level reduction or loss of response at two adjacent f_2 frequencies at some point during treatment, and comprise the DPOAE Hit group. The remaining ears (18 of 82 or 22%) did not experience significant reductions in DPOAE level and comprise the DPOAE Miss group. Observations that DPOAEs were sometimes unable to be recorded or did not show ototoxic changes indicate that DPOAE testing was less sensitive to ototoxicity than the behavioral test method used.

Factors Affecting DPOAE Sensitivity

Drug type • It was not known a priori whether DPOAE sensitivity would depend on the type of ototoxic drug administered. For example, DPOAEs might be more sensitive to cisplatin, which preferentially damages outer hair cells (Hodges & Lonsbury-Martin, 1999), compared with carboplatin, which results in a greater mix of inner hair cell and outer hair cell loss (Hofstetter, et al., 1997). Figure 4 shows hit, miss, and no response rates for DPOAEs as a function of the type of drug administered. Despite greater DPOAE hit rates for ears treated with ototoxic antibiotics, the type of drug administered was not significantly related to DPOAE sensitivity (Yates-corrected Chi-square test = 5.837, 2df, $p = 0.054$). Data were, therefore, collapsed across treatment groups for the remaining analyses. However, because of the small number of subjects exposed to carboplatin and ototoxic antibiotics in this study, this outcome must be interpreted with caution.

Magnitude of threshold shifts • Previous studies have shown that errors in dichotomous decisions regarding hearing status (normal versus impaired hearing) using DPOAE testing are more likely to occur for ears with mild than moderate or severe losses (Gorga, et al., 1996, 1997). Thus, it was hypothesized that errors in decisions regarding hearing change based on DPOAEs would depend on the magnitude of postexposure threshold shifts, with fewer errors associated with larger hearing changes.

Because threshold shifts typically occurred within the SRO, postexposure threshold shifts for behavioral SRO frequencies were normalized to each subject's highest audible frequency, F, with data plotted in Figure 5. Separate panels are for the

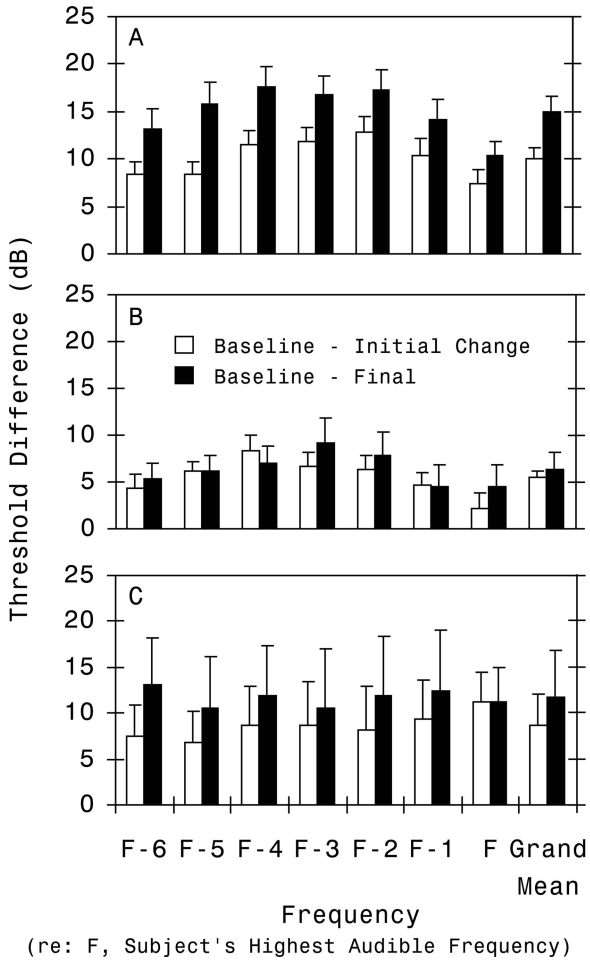

Fig. 5. Threshold shifts for behavioral SRO frequencies plotted separately for (A) the DPOAE Hit group, (B) Miss group, and (C) No Response group. SRO frequencies are normalized to each subject's highest audible frequency, *F*, which was defined during the baseline test. Thus, *F*-1 is 1/6-octave below *F*, *F*-2 is 1/6-octave below *F*-1, and so on. Threshold shifts are shown for the first test when significant hearing changes were noted (open bars) and for the final test obtained (filled bars). Error bars report standard errors.

DPOAE Hit group (panel A), Miss group (panel B), and No Response group (panel C). Behavioral threshold shifts are shown for the first test when significant hearing changes were noted (open bars) and for the final test obtained (filled bars). The SRO is by definition, a range of frequencies that at baseline, elicits measurable responses. Thus, all patients had SRO behavioral thresholds within the limits of the equipment at baseline. However, if ototoxic insult elevated behavioral thresholds beyond the equipment limitations, then thresholds were arbitrarily set to 120 dB SPL for difference calculations. Error bars represent one standard error.

Grand mean threshold shifts for DPOAE Hit, Miss, and No Response groups were determined by collapsing shifts across SRO frequencies and were examined for statistical significance using ANOVA. Grand mean shifts were significantly different by the final test date ($F = 3.747$, $p = 0.027$), and results of Bonferroni post hoc procedures indicated that these differences were between the DPOAE Hit group and the DPOAE Miss group ($p = 0.025$; grand mean difference = 8.9 dB, 95% CI: 0.9–17.0 dB).

By the final test date, threshold shifts at individual frequencies within the SRO ranged from 0.71 to 52.86 dB for the DPOAE Hit group (Fig. 5A, filled bars); mean threshold shifts were at least 10 dB across all SRO frequencies, and the grand mean shift was 15.54 (SEM = 1.64). Threshold shifts were comparatively smaller at the final test for the DPOAE Miss group, ranging from 0.71 to 34.29 dB (Fig. 5B, filled bars). Mean shifts at individual SRO frequencies never reached 10 dB, and the grand mean shift was just 6.62 (SEM = 1.80). Two of the 18 ears in which DPOAE missed behaviorally documented ototoxicity averaged threshold shifts greater than 10 dB. Respectively, these two ears (from separate subjects) demonstrated 14 and 34 dB threshold shifts averaged across the SRO. In contrast to the DPOAE Miss group, threshold shifts obtained for the DPOAE No Response group were not significantly different compared with those obtained for the DPOAE Hit group ($p = 0.442$). Patients with sufficient hearing loss to preclude effective monitoring using DPOAEs experienced substantial ototoxic threshold shifts when measured behaviorally.

Degree of pre-exposure hearing loss • Evidence from previous studies indicates that DPOAEs are often early indicators of ototoxic hearing loss, meaning that DPOAE changes occur even in the absence of clinically significant changes in hearing (Katbamna, et al., 1999; Mulheran & Degg, 1997; Stavroulaki, et al., 2002). Therefore, the magnitude of ototoxic threshold shifts alone might not be expected to account for DPOAE sensitivity to ototoxic damage. It was hypothesized that the degree and configuration of any pre-exposure hearing loss would also affect DPOAE sensitivity.

In Figure 2, mean pre-exposure pure-tone thresholds are shown for the entire sample of 90 ears. All but 17 of 90 ears (18.9%) had at least a mild, high frequency hearing loss before drug exposure. The majority of ears (69/90 or 76.7%) had mild to moderate hearing loss within the conventional frequency range and the few remaining ears (4/90 or 4.4%) had moderate to moderately-severe hearing loss. In Figure 6, mean pre-exposure pure-tone thresholds are plotted separately for the DPOAE Hit group (filled circles), the DPOAE Miss group (open circles), and the DPOAE No Response group (asterisks). As expected, the DPOAE Hit group comprised the better-

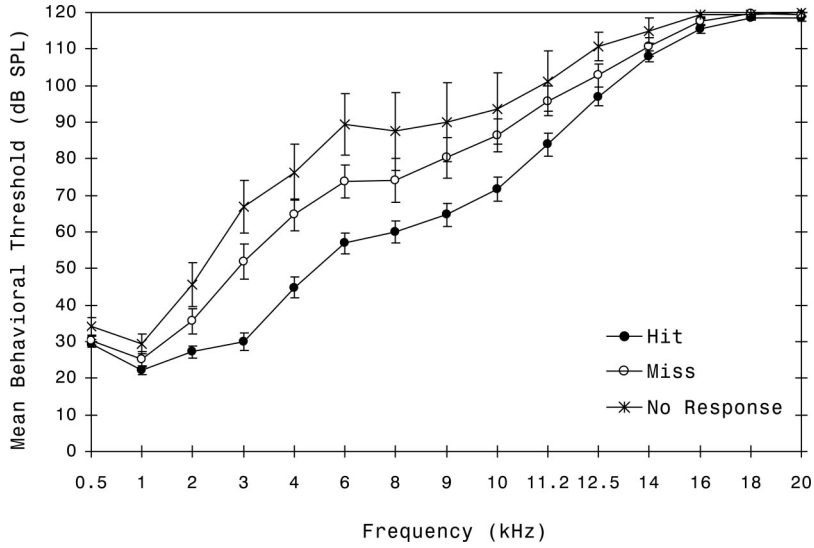

Fig. 6. Mean pre-exposure hearing thresholds in dB SPL. Separate curves are for DPOAE Hit (filled circles), Miss (open circles), and No Response groups (asterisks), respectively. Behavioral thresholds exceeding equipment limitations were set to 120 dB SL for mean calculations.

hearing ears in the sample. Thresholds at high frequencies define the behavioral high-frequency hearing limit (behavioral hf-limit) and this limit was similar for ears comprising DPOAE Hit, Miss, and No Response groups (Mann–Whitney U $p = 0.448$). The median and range for behavioral hf-limits are given in Table 3 for the DPOAE Hit, Miss, and No Response groups. Median values were reported in place of mean values because the underlying distribution of the data was predictably skewed.

To further investigate the relationship between pre-exposure threshold data and DPOAE sensitivity, behavioral threshold data were reduced by calculating the high-frequency pure-tone average (hf-PTA) for 2, 4, and 6 kHz (with data provided in Table 3). This frequency range corresponds to f_2 frequencies at which DPOAEs could be recorded in most of the normal-hearing subjects tested. Significant mean hf-PTA differences were found among the DPOAE Hit, Miss, and No Response groups ($F = 11.965$, $p < 0.01$). Bonferroni procedures applied post hoc indicated the mean hf-PTA was significantly lower (better) for the DPOAE Hit group (42.97 dB SPL, SD = 18.39) compared with either Miss (58.06 dB SPL, SD = 13.23) or No Response groups (70.42 dB SPL, SD = 19.92), with $p \leq 0.01$, for both post hoc comparisons. The lower bounds of the 5th to 95th percentile range for hf-PTA corresponding to the Miss group and No Response group were 51.48 and 53.77 dB SPL, respectively.

Configuration of pre-exposure hearing loss • DPOAEs could not always be measured at f_2's corresponding to the behavioral SRO, in part, because of the influence of elevated high-frequency thresholds associated with sloping hearing losses in the majority of subjects before drug exposure. The audiometric configuration near each subject's high-frequency hearing limit was quantified by calculating the difference in thresholds between the upper-frequency bound of the SRO (i.e., the behavioral hf-limit) and the lower-frequency bound of the SRO. The amount of this difference estimates a SRO threshold range, which provides information about the SRO slope. SRO threshold range describes the subject's hearing ability in the frequency range that is expected to change first, usually frequencies greater than 8 kHz. The degree of hearing loss reported earlier is a PTA (2, 4, and 6 kHz) restricted to the lower conventional frequencies. If a patient had a severe hearing loss (e.g., baseline behavioral

TABLE 3. Descriptive statistics by DPOAE group

	Hit	Miss	No Response
	Mean (SD)	Mean (SD)	Mean (SD)
2 kHz threshold (dB SPL)	27.2 (13.7)	35.6 (15.1)	45.6 (17.0)
4 kHz threshold (dB SPL)	44.8 (23.7)	64.7 (18.5)	76.3 (21.7)
6 kHz threshold (dB SPL)	56.9 (23.4)	73.9 (18.9)	89.4 (23.8)
hf-PTA (dB SPL)	43.0 (18.4)	58.1 (13.2)	70.4 (19.9)
SRO threshold range (dB)	40.9 (19.2)	28.1 (21.8)	24.4 (14.7)
	Median (range)	Median (range)	Median (range)
Behavioral hf-limit (kHz)	12.5 (3.6–20)	11.9 (4.5–14)	10 (3.6–14)
DPOAE hf-limit (kHz)	4.5 (1.0–7.9)	2.2 (1.7–5.6)	NA

hf-limit was 8 kHz) these two measurements would overlap; however most often these two measurements were different.

The mean SRO threshold range for the DPOAE Hit group was 40.94 dB suggesting that on average, the behavioral SRO region would have included frequencies with thresholds down to about 60 dB SPL. (Recall that the high-frequency limit has a threshold near 100 dB SPL by definition. Thus, 100 − 40.94 = 59.06). The mean SRO threshold range for the DPOAE Miss group and No Response group was 28.06 and 24.38 dB respectively, allowing on average for the lower bound of the SRO to have thresholds of about 70 to 75 dB SPL. Results of a one-way ANOVA suggest that these differences among groups were significant ($F = 4.905$, $p = 0.01$) and Bonferroni adjusted post hoc analysis indicated the significant differences were between the DPOAE Hit and Miss groups ($p = 0.015$) and between DPOAE Hit and No Response groups ($p = 0.026$).

Relationship between measurable DPOAEs and behavioral SRO • Another variable related to the degree and configuration of pre-exposure hearing loss is the highest f_2 resulting in a valid DPOAE. The median DPOAE high-frequency limit (DPOAE hf-limit) was significantly higher for the DPOAE Hit group (4.5 kHz; range 1.0–8 kHz) compared with the DPOAE Miss group (2.2 kHz; range 1.7–5.6 kHz) based on results of a Mann–Whitney U test ($p < 0.01$). In contrast, recall that median behavioral hf-limits were similar across groups (12.5 and 11.9 kHz, respectively for the Hit and Miss groups). Descriptive statistics are given in Table 3 for the hf-PTA, threshold range of the SRO, and high-frequency limits of behavioral threshold and DPOAE amplitude responses.

The relationship between the DPOAE hf-limit and the lower bound of the behavioral SRO is shown in Figure 7 for ears comprising the DPOAE Hit group (open bars) and the DPOAE Miss group (filled bars). Frequency separation is indicated in this figure using a histogram with 1/2-octave bins. In general, results indicate that the closer the DPOAE hf-limit was to the behavioral SRO, the greater the likelihood that DPOAEs changed following ototoxic insult. Frequency separation greater than two octaves resulted in a DPOAE hit rate approximately equal (5% versus 6%) to the expected false positive rate for the DPOAE change criterion used (as described in the Methods).

The amount of separation between the DPOAE hf-limit and the behavioral SRO was significantly associated with DPOAE sensitivity to ototoxic hearing changes (Pearson Chi-square $p = 0.036$), and this association was linear (Mantel-Haenszel Chi-square test of trend $p = 0.002$), suggesting as the amount of separation increased between the DPOAE hf-limit and the behavioral SRO, so did the percentage of ears whose DPOAE measures missed the behavioral hearing change. These data were dichotomized at each frequency separation to determine odds ratios to estimate the amount of frequency separation that rendered DPOAE testing less effective for ototoxicity monitoring. Four dichotomized splits were compared (e.g., <0.5 octaves compared with ≥0.5 octaves; ≤1 octave compared with >1 octave; and so forth).

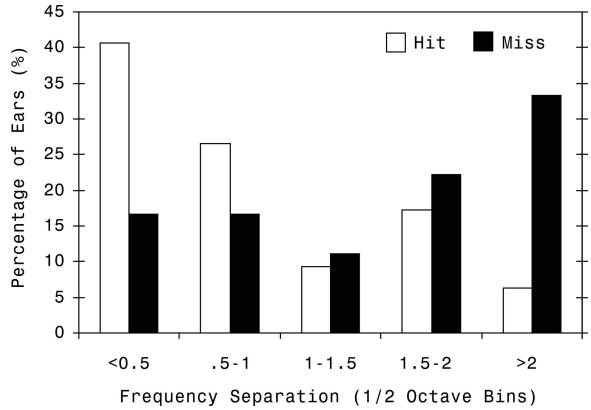

Fig. 7. Percentage of ears in DPOAE Hit group (open bars) and DPOAE Miss group (filled bars) as a function of the frequency separation (in ½-octave bins) between the DPOAE hf-limit and the lower bound of the behavioral SRO.

The resulting odds ratios were 3.42 (95% CI: 0.90–13.02), 4.10 (95% CI: 1.35–12.43), 4.08 (95% CI: 1.37–12.21), and 7.50 (95% CI: 1.83–30.68) for dichotomized splits at 0.5, 1, 1.5, and 2 octaves, respectively. A 95% CI is the interval that with 95% certainty contains the true population value as it might be estimated from a much larger study. If the 95% CI of the odds ratio includes 1, then no relationship is assumed. The dichotomized split at a 0.5 octave did not indicate any increased likelihood for missing behavioral hearing changes; however, dichotomized splits at 1, 1.5, or 2 octaves did indicate a greater likelihood of missing a hearing change, suggesting that the critical frequency separation between the DPOAE hf-limit and the behavioral SRO is about 1 octave. The odds of missing a hearing change when the frequency separation was greater than 1 octave were four times the odds of missing a hearing change when the frequency separation was less than one octave. Hearing changes were 7.5 times more likely to be missed when the amount of frequency separation was greater than two octaves.

The DPOAE hf-limit was further evaluated to estimate the limit, below which DPOAE testing was ineffective for ototoxicity monitoring. To determine the frequency at which to dichotomize DPOAE hf-limit for further analysis, quartiles of each group (Hit and Miss) were considered. The Hit group's 1st,

2nd, and 3rd quartiles were 2.8, 4.4, and 5.6 kHz, respectively. The Miss group's 1st, 2nd, and 3rd quartiles were 1.8, 2.2, 2.5 kHz, respectively. The quartiles indicate that at least 75% of the Hit group's DPOAE hf-limit is greater than 2.5 Hz and 75% of the Miss group's DPOAE hf-limit is at 2.5 Hz or below. Therefore, it was decided to categorize DPOAE hf-limit with a dichotomous split at this frequency. Based on this categorization, 77.8% (14/18) of DPOAE misses had DPOAE hf-limit at or below 2.5 kHz and 81.3% (52/64) of DPOAE hits had DPOAE hf-limit above 2.5 kHz. A Chi-square analysis was highly significant suggesting the Hit group was more likely to have a DPOAE hf-limit greater than 2.5 kHz compared with the Miss group ($\chi^2 = 22.606$, $p < 0.01$). The odds of showing DPOAE changes (hit) when the DPOAE hf-limit is greater than 2.5 kHz are 15.17 (95% CI: 4.23–54.34) times the odds of showing a DPOAE change when the DPOAE hf-limit is less than 2.5 kHz.

Toward Building a Model to Predict DPOAE Sensitivity

Any variable whose univariate test as described above had a $p < 0.25$ was a candidate for the multivariate model used to predict DPOAE sensitivity to ototoxic behavioral hearing changes. The initial main effects model included the continuous variables: (1) hf-PTA, (2) threshold range of the behavioral SRO; and the categorical variables formed by varying dichotomous splits, (3) DPOAE hf-limit, and (4) frequency separation between DPOAE hf-limit and the lower bound of the SRO. Variables were eliminated from the model through backward step-wise regression. Within the multivariate model, each independent variable was verified and only variables with significance at a 0.05 level were retained. All variables fell out of the model with the exception of DPOAE hf-limit ($p < 0.001$). The model was assessed for goodness-of-fit. The value of the Hosmer-Lemeshow goodness-of-fit test ($\chi^2 = 5.253$ with 8df, $p = 0.730$) suggested the model fit was adequate and the observed and expected values were in very close agreement. These results suggest that a single variable, DPOAE hf-limit, which can be obtained at the baseline evaluation, may be able to predict the success of ototoxicity monitoring with DPOAEs. For the f_2 range examined here (0.8–8 kHz), DPOAEs greater than 2.5 kHz were the best predictors of ototoxicity.

Timing of DPOAE Changes Relative to Behavioral Threshold Changes

As described in the Methods, initial DPOAE level changes did not always correspond in time with initial behavioral threshold changes. Therefore, sensitivity was also examined in terms of the relative timing of DPOAE and behavioral changes. In 21/64 or 32.8% of ears, the test session corresponding to a significant DPOAE change preceded the behavioral change on average by 55.5 days (SD = 60.4; range, 1–196 days). The same proportion of ears (21/64 or 32.8%) demonstrated initial DPOAE and behavioral changes during the same test session. Finally, for 22/64 or 34.4% of ears showing DPOAE changes, these DPOAE changes lagged behavioral changes by 63.9 days on average (SD = 64.2; range, 1–212 days). Variables that were significantly associated with DPOAE sensitivity were hf-PTA, threshold range of the behavioral SRO, DPOAE hf-limit, and frequency separation between DPOAE hf-limit and the lower bound of the SRO. These variables were further analyzed using the appropriate parametric (ANOVA) or nonparametric (Chi-square) test to examine the relative timing of DPOAE and behavioral changes following ototoxic drug exposure. However, significant group mean differences were absent at an alpha level of 0.05 for each independent variable examined.

DISCUSSION

Summary

This study evaluated aspects of pre-exposure audiograms and DPOAEs that might influence whether DPOAEs measured in a particular subject resulted in a hit (i.e., detection of hearing change) or a miss (failure to detect hearing change). The type of drug administered and the magnitudes of the ototoxic changes in pure-tone thresholds were also evaluated for potential effects on DPOAE sensitivity. Finally, a model was explored to determine which variables were the most predictive of DPOAE sensitivity to ototoxic hearing changes occurring near each subject's high-frequency hearing limit. DPOAE level changes were evaluated in adult subjects who experienced significant hearing changes after therapeutic treatment with ototoxic drugs. DPOAEs were considered to have changed if DPOAE level decreased at any two adjacent test frequencies during any postexposure test session.

The major results of this study are reviewed below. These results may have implications for the interpretation of DPOAEs in patients being monitored for ototoxicity and for predicting, a priori, which patients may be effectively monitored using DPOAEs.

1. DPOAEs were less sensitive to ototoxic damage compared with behavioral testing that included both conventional audiometric frequencies and 1/6-octave frequencies within an octave frequency range bounded by each patient's high-frequency hearing limit. The DPOAE hit rate was 78% in ears with con-

firmed behavioral threshold changes and measurable DPOAEs.
2. DPOAE sensitivity to ototoxicity was considered to be unrelated to the type of drug administered in the subjects sampled. However, the majority of subjects in this study were treated with cisplatin. Comparatively small samples of subjects treated with carboplatin and ototoxic antibiotics may have inflated the type II error rate, making it less likely that effects of drug type would be detected.
3. Factors that affected DPOAE sensitivity were the magnitude of postexposure threshold shifts (for ears with measurable DPOAEs, ototoxic threshold shifts missed by DPOAE testing were small on average); the degree and configuration of pre-exposure hearing loss (hearing loss imposed a limit on the range of DPOAE f_2 frequencies that could be monitored and this range did not always overlap with the range of frequencies showing changes in hearing); and the high-frequency limit of DPOAEs present at baseline (better sensitivity was achieved for ears with measurable DPOAEs at higher frequencies).
4. Multiple regression analysis was used to build a model to determine the best combination of predictors for DPOAE sensitivity to ototoxic threshold shifts. DPOAE high-frequency limit greater or equal to 2.5 kHz was the only variable that was retained in the model.
5. DPOAE level changes did not always correspond in time with initial behavioral threshold changes. A roughly equal proportion of ears showed DPOAE changes before (33%), concurrent with (33%), and after (34%) initial behavioral hearing changes. None of the variables examined in this study were able to explain differences in the relative timing of DPOAE and behavioral changes.

DPOAE Changes are Associated with Hearing Changes at Higher Frequencies

Results from the present study indicate that ototoxic-induced DPOAE changes can occur at frequencies lower than those showing behavioral threshold changes, but that DPOAEs more than about an octave below frequencies showing behavioral changes have limited predictive value. These results are generally consistent with evidence that levels of DPOAEs (Arnold, et al., 1999) and stimulus-frequency (SF) OAEs (Avan, et al., 1993; Ellison & Keefe, 2005) correlate significantly with pure-tone thresholds obtained at comparatively higher frequencies. Though greater correlations are often found between behavioral thresholds and OAEs obtained at the same frequency compared with disparate frequencies (Ellison & Keefe, 2005), it has been demonstrated that high-frequency hearing does impact comparatively lower frequency emissions. Arnold et al. (1999) found that a pure-tone average (PTA) of frequencies from 11.2 to 20 kHz accounted for 14% of the variance in DPOAE levels from f_2 = 4 to 8 kHz in normal-hearing adults. PTA in the conventional frequency range was correlated with age and the extended high-frequency PTA. However, when conventional PTA, extended high-frequency PTA and age were modeled together, extended-high frequency hearing exclusively explained DPOAE variability measured at lower frequencies. Similarly, Avan et al. (1993) found correlations between hearing thresholds and more apically generated SFOAEs occurring about one octave below.

In the present study, changes in DPOAEs occasionally occurred in the presence of hearing changes at remote frequencies, however, the odds of missing a hearing change when DPOAEs were greater than one octave from the behavioral SRO were four times the odds of missing a hearing change when this frequency separation was less than one octave. Hearing changes were 7.5 times more likely to be missed when the amount of frequency separation was greater than two octaves, and the associated hit rate for this frequency separation was equivalent to the estimated false positive rate for the DPOAE change criteria used (about 5%).

Factors Affecting the Sensitivity of Behavioral and DPOAE Testing

Of clinical relevance is the observation from the current study that DPOAE sensitivity to ototoxic hearing changes depends on the magnitude of post-exposure threshold shifts. For ears producing sufficiently robust DPOAEs to be monitored, ototoxic threshold shifts missed by DPOAE testing were small on average (<7 dB). This finding is encouraging, suggesting if DPOAEs do not change by the criterion amount following the administration of ototoxic drugs, subjects would be expected to experience less behavioral hearing change than if the DPOAEs do change. However, losses missed in one subject averaged 34 dB within the SRO frequency range. The potential for large hearing shifts to be missed by DPOAEs in individual subjects suggests that there is use in determining factors that may cause such misdiagnoses.

DPOAE sensitivity may depend on age and pre-exposure hearing status, variables which are often correlated. Effects of age were not examined in the current study. However, previous studies in which DPOAE testing was found to be more sensitive to

ototoxic damage compared with behavioral pure-tone threshold testing were mostly studies of aminoglycoside ototoxicity in young subjects with good pre-exposure hearing (e.g., Mulheran & Degg, 1997; Stavroulaki, et al., 2001). Current observations show that DPOAEs may fail to diagnose changes in hearing if pre-exposure hearing is poor. For the group of subjects in which DPOAEs were able to be monitored, but failed to detect ototoxic hearing changes, the lowest SRO frequency (e.g., the frequency one octave below the SRO high-frequency limit) had a threshold level greater than about 70 dB SPL, which would have precluded DPOAE measurement at SRO frequencies. DPOAEs also often failed to detect hearing changes or were absent for ears in which the behavioral threshold pure-tone average of 2, 4, and 6 kHz was greater than about 50 dB SPL. This is consistent with evidence from many previous studies showing that DPOAEs are often absent for ears with moderate or greater hearing loss (Gorga, et al., 1996, 1997).

DPOAE sensitivity was associated with DPOAE preset for higher f_2's. The odds in favor of detecting a hearing change when DPOAE hf-limits are greater than 2.5 kHz is 15 times that for DPOAE hf-limits less than 2.5 kHz. In the present study, many ears with DPOAE limits around 2.5 kHz had moderate hearing loss at 2 kHz, gradually sloping to greater degrees of hearing loss above 2 kHz. DPOAE sensitivity in such ears may have suffered because the frequencies at which DPOAEs could be recorded were remote from those frequencies showing initial ototoxic hearing shifts, and because DPOAEs below 2 kHz are more likely to be contaminated by noise compared with frequencies above 2 kHz (Gorga, et al., 1993, 1997). Results of logistic regression modeling suggest that DPOAE high-frequency limit, a single variable obtained at the baseline evaluation, is indicative of the effectiveness of ototoxicity monitoring using DPOAEs.

Use of higher intensity stimuli to evoke DPOAEs may have resulted in a greater number of ears having DPOAEs over a wide frequency range. However, a large proportion of ears (91%) was able to be monitored in the current study using DPOAEs elicited by L_1/L_2 primary levels = 65/59 dB SPL. For comparison, Ress et al. (1999) found that in adult subjects, many of whom had pre-exposure hearing loss, DPOAEs could be elicited in a slightly smaller proportion (82%) of ears at baseline using L_1/L_2 primary levels = 75/75 dB SPL. Further, use of higher-level stimuli may not have improved DPOAE test performance because hearing losses greater than about 60 dB are not well correlated with DPOAE levels (Gorga, et al., 1997). Such losses are often attributed to inner hair cell or spiral ganglion cell damage, and such damage would not be expected to be correlated with DPOAEs (auditory nerve: Martin, et al., 1987; Siegel & Kim, 1982; inner hair cell: Trautwein, et al., 1996). In adult subjects, DPOAE sensitivity rates were similar when obtained previously using higher-level primaries (Ress, et al., 1999) compared with the somewhat lower levels used in the present report.

There remains a possibility that DPOAEs are more sensitive to ototoxicity caused by ototoxic antibiotics than to the other ototoxic drugs examined. In the current study, DPOAEs changed significantly in all of the ears sampled from subjects receiving ototoxic antibiotics, but statistical analyses did not show an effect of drug type on DPOAE sensitivity. Cisplatin was the drug received by the majority of subjects in the current study. Comparatively small samples of subjects treated with ototoxic antibiotics and carboplatin may have inflated the type II error, making it less likely that effects of drug type would be significant in current analyses. Further research with greater sample size is needed to validate this finding.

The relative sensitivity of DPOAEs to behavioral hearing change is influenced by the behavioral monitoring technique used. Ototoxic hearing changes in this report were examined using a measurement technique that targets the frequency range most vulnerable to ototoxic damage (the "Sensitive Range for Ototoxicity, SRO"). The frequency range that shows ototoxic changes first resides within one-octave of a subject's operationally-defined high frequency hearing limit determined before exposure to ototoxic drugs (Fausti, et al., 1999; Vaughan, et al., 2002). This SRO may be within the range of frequencies tested using conventional audiometry or using ultra-high-frequency audiometry, depending on a subject's pre-exposure hearing ability. In the present study, all subjects could be tested using this behavioral monitoring technique and 92% of subjects had significant pure-tone threshold shifts within the SRO using ASHA (1994) threshold-shift criteria.

In contrast, evidence from previous studies showing that DPOAE testing is more sensitive to ototoxic damage compared with behavioral testing is based largely on studies using pure-tone threshold testing with one- or 1/2-octave precision confined to the conventional frequency range extending up to 8 kHz (e.g., Mulheran & Degg, 1997; Stavroulaki, et al., 2001, 2002). Subjects in these studies were children or young adults with good pre-exposure hearing. High-frequency hearing limits in these young subjects likely exceeded 8 kHz, potentially by more than an octave if high-frequency hearing up to 20 kHz was intact. This would place the SRO outside of the frequency range monitored, thus reducing the efficacy of behavioral ototoxicity monitoring compared with the technique used in the present report.

Consistent with this view, monitoring protocols using only conventional frequency testing have been shown to be less sensitive compared with protocols that incorporate pure-tone threshold testing above 8 kHz, usually in 1/6-octave frequency steps (Fausti, et al., 1992, 1999, 2003). In addition, a previous study in adult subjects treated with cisplatin found that ototoxicity detection rates were greater when obtained using DPOAEs compared with conventional audiometric testing, similar to the results obtained in young subjects. However, ototoxicity detection rates in adult subjects were similar for DPOAEs compared with ultra-high frequency audiometric testing using 1/6-octave precision (Ress, et al., 1999). The current study extends these results by showing that regardless of subject's ability to hear at ultra-high frequencies, behavioral testing near each subject's high-frequency hearing limit is more sensitive compared with DPOAE measures which can not be obtained in all subjects, and can be obtained only over a narrow frequency range in other subjects.

At least one study has reported group differences in DPOAE responses in the absence of hearing differences measured at conventional and ultra-high frequencies (Katbamna, et al., 1999). Recall that Katbamna and colleagues looked for differences in pure-tone hearing and DPOAE measurements in a group of normal hearing children and adolescent subjects with a history of tobramycin exposure and compared them to drug-free counterparts. DPOAE variables examined were DPOAE amplitude (i.e., DP-grams), latency, and I/O function threshold. Group differences were found for DPOAE latency and I/O growth functions, but not for DPOAE level differences taken from DP-gram data. It is beyond the scope of this report to evaluate differences in the sensitivity of particular DPOAE decision variables measured. However, it is possible that monitoring DPOAE latencies and/or detection thresholds would have increased DPOAE sensitivity to ototoxicity compared with the monitoring of DPOAE response level at a fixed, moderate stimulus level.

Further research is needed to compare DPOAE decision variables and change criteria to optimize DPOAE test performance for early detection and monitoring of ototoxicity. This research could involve the construction of receiver operating characteristic curves, which show the trade off between true positive rates (sensitivity) and false positive rates (1-specificity) for a series of criterion cut-off values. Because of the concern that DPOAE changes may occur at a stage when ototoxic damage has not yet affected behavioral thresholds (i.e., damage is "preclinical"), true positive and false positive rates could be defined using separate sample populations: drug-exposed subjects and hospitalized control subjects, respectively (Dobie, 2005). Such information would improve the ability of clinicians to make informed clinical decisions about whether or not ototoxic damage has occurred, when such decisions must be based primarily on DPOAE results.

Relative Timing of DPOAE and Behavioral Ototoxic Changes

DPOAE changes in the current study lagged behavioral changes at SRO frequencies in about one-third of the ears examined. None of the variables examined that were associated with DPOAE sensitivity to ototoxic hearing loss provided insight into the time when DPOAE changes would first be observed relative to the time when behavioral changes are first detected. The lack of statistical association may be a result of sample size and is worthy of further investigation. It is encouraging that in previous studies, OAEs detected ototoxic damage at least as early as did behavioral test methods in children and young adults with good pre-exposure hearing (Stavroulaki, et al., 2001, 2002). Furthermore, measures of DPOAE amplitude may not be the best clinical indicator of ototoxicity in certain patient populations.

CONCLUSION

In general, results suggest that DPOAE testing is a useful screening tool for ototoxicity in adults with pre-exposure hearing loss, but may be less sensitive compared with a behavioral test method that targets thresholds near the upper limit of a subject's audible frequency range. Hearing changes missed using DPOAE testing generally were small. Results also indicate that successful monitoring of ototoxicity with DPOAEs depends on the measurable DPOAE f_2 frequency range and its relation to the highest behavioral test frequencies. Ototoxic-induced DPOAE changes can occur at frequencies lower than those showing behavioral threshold changes, but DPOAEs more than approximately one octave below frequencies showing behavioral changes have limited predictive value. A single variable obtained at baseline may help assess whether ototoxicity monitoring with DPOAEs will be successful.

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