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Objective Measures of Ototoxicity

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A leading cause of preventable sensorineural hearing loss is therapeutic treatment with medications that are toxic to inner ear tissues, including certain drugs used to fight cancer and life-threatening infectious diseases. Ototoxic-induced hearing loss typically begins in the high frequencies and progresses to lower frequencies as drug administration continues (Campbell & Durrant, 1993; Campbell et al., 2003; Macdonald, Harrison, Wake, Bliss, & Macdonald, 1994). It is important to detect ototoxicity before damage occurs to the region of hearing < 4 kHz, which is important for speech perception (De Paolis, Janota, & Frank, 1996). Sensitive and time-efficient behavioral techniques have been developed to monitor high-frequency (> 8 kHz) hearing to detect ototoxic-induced changes before damage has progressed to lower frequencies (Fausti et al., 1999). Hearing thresholds obtained through behavioral audiometry are the current gold standard for detecting ototoxic-induced changes in hearing. However, behavioral techniques are not effective for a large population

of patients who are unable to provide reliable responses; subsequently, many of these patients do not receive monitoring for ototoxic-induced changes in their hearing. The development of objective measures that do not require patient cooperation is necessary to monitor all patients receiving ototoxic drugs.

Two objective measures offer promise in their ability to detect and to monitor hearing changes caused by ototoxicity: auditory brainstem responses (ABRs) and otoacoustic emissions (OAEs). ABRs are an objective, pre-behavioral measure of neural responses in the brainstem that reflect hearing function. OAEs are an objective, pre-behavioral measure of cochlear mechanical responses that reflect cochlear outer hair cell function. After middle ear dysfunction has been ruled out, OAEs may be an excellent indicator of early ototoxic damage. Abnormal middle ear function and baseline hearing loss greater than about 40 dB HL may preclude effective monitoring using OAEs. Use of ABR testing may be more appropriate in such cases.

Changes in hearing can be identified by these techniques when monitoring patients before, during, and after drug treatment.

A common use of ABRs and OAEs is the detection of hearing loss in neonatal hearing screenings (Cone-Wesson, Kurtzberg, & Vaughan, 1987; Hall, Smith, & Popelka, 2004; Jacobson & Jacobson, 2004; Norton et al., 2000; Sininger, Abdala, & Cone-Wesson, 1997). These measures require no behavioral response and can be recorded in sleeping patients. Assuming these measures correctly identify changes in hearing sensitivity, ABR and OAE testing is amenable to ototoxicity monitoring of patients who cannot provide reliable responses to behavioral hearing testing (e.g., infants and sick patients). Currently, there are no accepted clinical protocols or criteria for ototoxic change using objective measures of ototoxicity. A barrier to the widespread use of ABR and OAE for ototoxicity monitoring is related to this lack of standardized monitoring procedures. Use of various testing protocols, different ototoxic change criteria, and different patient populations in ototoxic studies has hindered the translation of research results into clinical practice. The following review focuses on ABR and OAE test-retest variability in subjects not receiving ototoxic drugs. Such studies provide the basis for developing objective protocols for monitoring ototoxic damage. Further research is needed to validate these results in large groups of subjects receiving ototoxic drugs.

Despite the lack of standardized protocols, ABRs are currently being used to monitor auditory brainstem activity before, during, and after drug treatment and offer the possibility of detecting early changes in ototoxicity for very sick patients. Changes in the ABR were concomitant with diminishing hearing in neonatal patients receiving aminoglycoside antibiotics (Bernard, Pechere, & Hebert, 1980) and adult patients receiving the chemotherapeutic agent cisplatin (De Lauretis, De Capua, Barbieri, Bellussi, & Passali, 1999). ABR changes have been characterized by a significant prolongation of wave latency or the disappearance of a wave that was present previously.

Use of the ABR to detect hearing changes caused by ototoxicity in humans has been limited to standard (square wave) click-evoked responses (De Lauretis et al., 1999), time-consuming derived-band responses (Coupland, Ponton, Eggermont, Bowen, & Grant, 1991) or primarily recorded in infants at risk for ototoxic-induced hearing loss (de Hoog et al., 2003). Standard click-evoked ABRs provide information regarding the normalcy of the peripheral auditory system in response to a broad-spectrum signal, but provide little information regarding high-frequency hearing where the earliest ototoxic changes occur. In order to detect the ear-

liest ototoxic changes, it is necessary to use high-frequency stimuli to elicit the ABR (Stapells & Oates, 1997). The detection of hearing change at frequencies > 8 kHz can provide valuable information regarding individual susceptibility to ototoxicity. This early detection of ototoxicity makes it possible to prevent the progression of hearing loss to lower frequencies where speech perception can be greatly impaired. The key to detecting hearing changes in patients at risk for ototoxicity is serial monitoring (i.e., before, during, and after drug treatment; Campbell et al., 2003). Thus, it is imperative that the measure used to detect ototoxicity is reliable over time.

The reliability of ABRs elicited by high-frequency stimuli has been studied extensively by Fausti and colleagues (Fausti, Frey, Henry, Olson, & Schaffer, 1992; Mitchell, Fausti, & Frey, 1994; Fausti et al., 1995; Henry, Fausti, Kempton, Trune, & Mitchell, 2000; Mitchell, Ellingson, Henry, & Fausti, 2004). The following is a brief review of that body of work. First, the use of single, high-frequency tone bursts to elicit ABRs will be examined, followed by the use of multiple, high-frequency tone bursts chained together, and the use of single, high-frequency broadband clicks will be discussed.

Fausti and colleagues (1991) first established the test-retest reliability of ABRs elicited by high-frequency tone bursts in listeners with normal hearing using high-frequency tone bursts (8, 10, 12, and 14 kHz) presented at a rate of 11.1/s. Each ABR was obtained twice to ensure within-session reliability. These ABRs were compared to both behavioral thresholds and standard click-evoked ABRs. No significant differences within an individual subject across session were found for waves I and V. Absolute mean differences ranged from < 0.01 ms to 0.05 ms across frequencies.

Once the test-retest reliability of high-frequency tone burst ABRs was established, Fausti and colleagues (1992) applied the method to 34 patients receiving ototoxic drugs. Again, tone burst ABRs were recorded at 8, 10, 12, 14 kHz in addition to a standard click-evoked ABR. Patients underwent serial monitoring with the decision criteria for ABR change defined as (a) a 0.3 ms latency shift for wave I or wave V or (b) a scoreable response becoming unscorable. The researchers showed that the high-frequency tone burst ABRs identified 87.1% (27/31) of ears demonstrating a behavioral change in hearing sensitivity. Only 28.6% of these ears were detected by standard click-evoked ABRs. The results clearly showed the sensitivity of ABRs in detecting ototoxic change.

In a similar study (Fausti et al., 1995), ABRs elicited by a standard click and by tone bursts of 8, 10, 12,

and 14 kHz were obtained in 20 listeners with high-frequency hearing loss. Hearing loss was limited to thresholds of ≤ 25 dB HL from 0.25 - 1 kHz and ≤ 70 dB HL from 3 - 6 kHz. ABRs were obtained in two separate test sessions for each listener. ABR thresholds were obtained for each individual at each tone burst frequency where wave V could be identified. Stimulus levels were decreased from 120 dB peak SPL in 10 dB steps down to 40 dB peak SPL. ABR thresholds were defined as the lowest presentation level at which wave V could be identified. ABRs were reliably recorded at 8 and 10 kHz but were not often present at 12 and 14 kHz. As expected, the ABR wave V latencies for the tone burst stimuli were longer at each presentation level than the wave V latencies for the click. The average difference between the mean wave V latency for the 8 kHz tone burst and the mean wave V latency for the click was 0.85 ms. No significant difference in the slope of the latency intensity functions existed between the tone bursts and the click for the wave V latency. The researchers showed that high-frequency stimuli could elicit reliable ABRs.

Recording ABRs at several test frequencies and levels can require a considerable amount of time. In an attempt to decrease testing time, Mitchell and colleagues (1994) developed a technique to record ABRs from several frequencies organized in a single train or sequence. The first step in developing the ABR stimulus train was to determine where neural adaptation occurred as a function of stimulus level, stimulus frequency, and interstimulus interval. Adaptation would prolong peak wave latencies and potentially affect the test sensitivity and specificity. Mitchell recorded ABRs elicited by paired stimuli at 21 frequencies from 1 - 32 kHz in $\frac{1}{4}$ -octave steps with a rise/fall time of 1 ms and with interstimulus intervals (ISIs) of 3 - 30 ms. Wave IV (V in humans) was slightly delayed at higher intensities, suggesting longer neural recovery times for high level signals. Latency delays occurred less frequently for later waves than earlier waves and did not occur for ISIs of ≥ 10 ms. In addition, latency shifts were shorter if the frequency of the second tone burst was of a different frequency than the first tone burst. The frequency separation necessary to avoid adaptation for an ISI of 3 ms approached one octave. These data were used to develop high-frequency stimulus trains for use in humans.

Based on the adaptation study in the guinea pig, a multiple high-frequency tone burst stimulus train was developed to elicit the ABR for ototoxicity monitoring (Fausti, Mitchell, Frey, Henry, & O'Connor, 1994; Henry et al., 2000). The single tone bursts in the multiple frequency train were presented 10 ms apart. Each train was presented with 60 ms of silence between

trains. Responses recorded from the multiple-stimulus train were compared to responses recorded from the same stimuli presented as single tone bursts. Although responses to individual tone bursts presented in the train showed some adaptation compared to responses to tone bursts presented singly, the reliability of the ABR latencies were equivalent. The researchers showed that tone burst stimuli presented in a multiple-stimulus train produced reliable ABRs.

To further reduce the testing time, other stimuli were investigated. Using the results from the behavioral studies showing that a limited high-frequency range of about one octave appears most sensitive to early onset of ototoxicity (Fausti et al., 1999), a high-frequency stimulus was developed using digital signal processing to stimulate the cochlea over a wide-band of high frequencies with a single stimulus. Responses to this high-frequency click (8 - 14 kHz) were compared to those from high-frequency tone burst stimuli over the same range. It was observed further that high-frequency click responses were more robust than those to tone burst stimuli (Mitchell et al., 2004). Data from normal hearing subjects suggest that responses to the high-frequency "click" stimulus were as reliable as those generated with tone burst stimuli and conventional clicks both within and between test sessions.

To detect ototoxicity it is necessary to record a reliable response and to monitor the stability of that response over the course of drug treatment. Since ototoxic damage begins in the basal (i.e., high-frequency) region of the cochlea and progresses apically (i.e., low frequency), it is important to identify the highest frequency region where a reliable response can be recorded. Choosing a frequency or frequency region to monitor for hearing change is not a simple task. This problem is amplified for a patient who may have preexisting hearing loss that necessitates testing several frequencies to identify the highest frequency region producing a reliable response. To address this challenge, investigators within our laboratory are collecting ABRs using multiple, high-frequency, narrow-band clicks presented at multiple intensities and sequenced together in a single train. We anticipate these high-frequency click trains will allow for the rapid identification of a frequency range sensitive to ototoxicity in patients with pre-existing hearing loss that require an individualized approach to monitoring.

Evoked OAEs are low-level acoustic responses generated within the cochlea, transmitted through the middle ear system, and measured in the external ear canal. The presence of the OAE response, its amplitude (or level) and its latency depend upon the physiological status of the cochlear outer hair cell-system

and the middle ear apparatus (Konrad-Martin & Keefe, 2005; Gorga et al., 1993). Experimental administration of ototoxic drugs has its greatest effect on the cochlear outer hair cells and influences OAE responses in animals (Hodges & Lonsbury-Martin, 1998; Furst, Maurer, & Schlegel, 1995). A variety of acoustic signals are used to elicit OAEs. Transient-evoked OAEs (TEOAE) are elicited by broadband clicks or tone bursts. Distortion-product OAEs (DPOAEs) are elicited using two tones presented simultaneously. Emissions elicited by a single frequency are called stimulus frequency OAEs (SFOAEs).

In numerous reports, researchers have examined TEOAEs and DPOAEs in subjects receiving ototoxic drugs. They primarily addressed ototoxic changes in OAE levels within patient groups receiving aminoglycoside antibiotics as treatment for life-threatening infections (Hotz, Harris, & Probst, 1994; Littman & Emery, 1997; Mulheran & Degg, 1997; Katbamna, Homnick, & Marks, 1999; Stavroulaki et al., 1999; Stavroulaki, Apostolopoulos, Segas, Tsakanikos, & Adamopoulos, 2001) or receiving the platinum-based drug cisplatin as treatment for cancer (Zorowka, Schmitt, & Gutjahr, 1993; Ozturan & Lam, 1996; Allen, Gentry, Shipp, & Van Landingham, 1998; Ress et al., 1999; Lonsbury-Martin & Martin, 2001). OAE level changes in these studies have demonstrated OAE sensitivity to ototoxic damage.

The relationship between ototoxic OAE changes and ototoxic pure-tone threshold shifts is unclear at this time. In numerous studies, researchers have reported that OAE level changes preceded behavioral hearing changes in patients receiving ototoxic drugs, whether pure-tone thresholds were tested within the conventional frequency range (0.5 - 8 kHz; Katbamna, Homnick, & Marks, 1999; Stavroulaki et al., 1999; Stavroulaki et al., 2001; Mulheran & Degg, 1997; Ress et al., 1999) or included the ultra high-frequency range > 8 kHz (Lonsbury-Martin & Martin, 2001). The increased susceptibility of OAEs to ototoxic damage compared to behavioral testing may reflect DPOAE sensitivity to pre-clinical changes in cochlear outer hair cell function. In another study comparing behavioral testing within the ultra high-frequency range with DPOAE testing, effects of ototoxicity were observed in a similar proportion of ears using both techniques (Ress et al., 1999). Thus, DPOAEs may be sensitive to ototoxic damage at cochlear locations coding frequencies higher than the DPOAE eliciting tones (Arnold, Lonsbury-Martin, & Martin, 1999). Such evidence supports the potential use of OAE testing for the early detection of ototoxicity, which is known to occur first at high-frequency coding regions near the cochlear base. Results of case studies (Lonsbury-Martin, & Martin, 2001) and studies in groups of patients (Stavroulaki et al., 2001)

indicate that DPOAE sensitivity to ototoxic damage was more sensitive compared to TEOAEs elicited by clicks. TEOAEs were found to have greater sensitivity compared to ABR in a group of children receiving aminoglycoside antibiotics (Stavroulaki et al., 1999).

Test-retest reliability for OAE level is good when examined using serial measurements in subjects not receiving ototoxic drugs. Franklin, McCoy, Martin, and Lonsbury-Martin (1992) investigated test-retest reliability in DPOAE and TEOAE in order to establish the stability of emissions over time. One ear from 30 subjects was tested for 4 consecutive days and over 4 successive weeks to establish both short-term and long-term reliability. DPOAEs were collected from 1 - 8 kHz at 55, 65, and 75 dB SPL. DPOAE input/output (I/O) functions were collected at 1, 2, 3, 4, 6 and 8 kHz from 35 - 85 dB SPL in 5-dB steps. For all conditions, the two tones comprising the stimulus were presented with equal sound-pressure level (in dB). TEOAEs were elicited by a broadband click with an effective stimulus level of about 45 dB SPL at 1, 2, 3 and 4 kHz. Franklin used repeated-measures of analysis of variance to derive a reliability coefficient. Reliability was considered good if this value was greater than 0.85. In the majority of DPOAE and TEOAE conditions (across both levels and days/weeks), there was a high degree of correlation (> 0.8) between tests repeatedly administered to the same individual. The exceptions generally occurred at 1 kHz and at the lowest input level (35 dB SPL) for DPOAEs and at 4 kHz for TEOAE. This increased variance in DPOAE recordings was likely related to subject physiologic noise.

Another approach to quantify normal variance is to calculate the standard error of the measurement (SEM). The SEM is an estimate of the SD expected in repeated measures testing and the two can be treated similarly, such that $2 \times \text{SEM}$ will estimate 95% of the true emission variance. For the majority of stimulus conditions, Franklin and colleagues (1992) found that the SEM was less than 2 dB and 3 dB for DPOAE and TEOAE, respectively. Again, DPOAE at 1 kHz and the lowest input levels, and TEOAE at 4 kHz showed the greatest variability with SEM values ranging 5-7 dB.

Further efforts were made to quantify the effects of signal-to-noise ratios (SNR) on the test-retest reliability of DPOAE by Beattie, Kenworthy, and Luna in 2003. In this study, one ear from 50 female subjects with normal hearing was tested under three conditions: immediate test-retest with no delay and no repositioning of the probe between tests, very short-term test-retest with a 10- to 20-minute break and re-insertion of probe between tests, and short-term test-retest with 5-10 days

between tests. The primary tones f_2 and f_1 were presented at equal sound pressure levels ($L_1=L_2$) of 65 dB for all frequencies and with $f_2/f_1=1.19$ for 500 Hz and $f_2/f_1=1.21$ for 1, 2, and 4 kHz. Data collection was programmed to stop once SNR reached nominal levels of 3, 6, or 12 dB with a minimum of five averages. Beattie derived SEM values at each SNR, frequency, and time interval to assess test-retest reliability. The standard errors across time intervals and frequencies at each SNR were approximately the same and had no substantial effects on test-retest reliability, because few of the recorded SNR actually fell below 11 dB. There was, however, a frequency interaction similar to that reported by Franklin and colleagues (1992), in that the lowest DPOAE frequency (0.5 kHz) was more variable than the higher frequencies recorded and was likely related to increased noise. The SEM collapsed across SNR and time intervals at 0.5 kHz was about 4.6 dB, nearly twice as large as the standard error found at the higher frequencies, 1 – 4 kHz, which yielded a combined SEM of about 2.5 dB.

Beattie and colleagues (2002) also calculated the SEM of the difference between serial OAE measurements (SEM_{Δ}). They argued that the SEM_{Δ} was the statistic best suited for determining whether sets of OAE measurements (e.g., OAEs measured before and after ototoxic drug administration) differed significantly. Based on their SEM_{Δ} results, Beattie found that to be a significant change, the OAE level difference needed to exceed approximately 14 dB at 0.5 kHz and 7 dB between 1-4 kHz to indicate a true change in the measurement.

Roede, Harris, Probst, and Xu (1993) proposed that clinically relevant changes to OAE measurements obtained over time should exceed the mean amplitude test-retest differences plus 2-standard deviations (i.e., exceed 95% of expected normal variability). To determine DPOAE change criteria, Roede analyzed 22 ears with normal hearing from 0.8 – 8 kHz with $f_2/f_1=1.21$ and primary tones presented at fixed equal levels ($L_1=L_2$) of 70 or 55 dB SPL. Input/output functions were also obtained at 0.8, 1, 1.5, 2, 3, 4, and 6 kHz ($f_2/f_1=1.22$) with L_1 stimulus level decreasing in 5-dB steps from 70 to 35 dB SPL and corresponding $L_2 = L_1 - 6$ dB SPL at each level. OAEs were obtained in four tests that generated five measurement time intervals at one week, 2 weeks, 4 weeks, 5 weeks, and 6 weeks. The researchers showed that the time intervals had no influence on OAE variability; however, variability was influenced by frequency and stimulus level. Similar to previous reports, test-retest differences were greater at low (<1 kHz) and high (≥ 6 kHz) test frequencies compared to the mid-frequencies tested. Variability also tended to increase with decreasing stimulus levels

such that at fixed equal levels of 70 and 55 dB SPL, mean variability collapsed across frequency was reported to be 1.8 and 2.9 dB, respectively. Comparably, the I/O functions revealed about 1.0 dB difference in mean variability between the highest (70 dB SPL) and lowest (40 dB SPL) recordable stimulus levels. Thus, Roede and colleagues determined that the OAE measurement difference between tests must exceed 5.4 dB (mean + 2SD) at stimulus levels of 70 dB SPL and 8.3 dB (mean + 2SD) at stimulus levels of 55 dB SPL to be clinically relevant.

Clinical use of criteria based on the OAE test-retest variability in subjects not exposed to ototoxic drugs is expected to result in few false positive responses; however, the sensitivity achieved using these particular criteria has not been determined within a large-scale clinical study. The OAE studies in our laboratory are aimed at determining the probability that a given OAE change predicts eventual behavioral changes in hearing. Other challenges to OAE monitoring currently being addressed in our laboratory include extending the recording of reliable emissions to the basal region of the cochlea (frequencies ≥ 8 kHz) where ototoxicity is known to present first. Results of these studies are expected to provide information about the temporal and frequency relationship between OAE and behavioral changes that reflect ototoxic damage.

Determining effective ototoxicity detection and monitoring strategies using objective measures of auditory function is an active area of research. ABR and OAE testing do not require patient attentiveness or cooperation; thus, these methods can assess ototoxic hearing changes in patients who are unable to provide reliable behavioral responses. These techniques have demonstrated reliability and sensitivity for early ototoxicity detection. DPOAEs appear to provide earlier detection compared to TEOAEs, ABRs, or behavioral measures of ototoxicity. However, OAEs may not be able to be monitored for change in patients with abnormal middle ear function or substantial hearing loss. The use of high-frequency narrowband ABRs to detect ototoxicity shows promise. ABRs offer the advantage that they can be used to predict hearing sensitivity in non-responsive patients. Use of well-accepted statistical methods for determining test performance in large groups of patients receiving ototoxic drugs and hospitalized (control) patients receiving non-ototoxic drugs are required in order to optimize ABR and OAE techniques for ototoxicity early detection and monitoring and to determine standard best practice methods. The primary use will be for patients who are unable to tolerate the demands of behavioral hearing test procedures.

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