Early Detection of Ototoxicity Using High-Frequency, Tone-Burst-Evoked Auditory Brainstem Responses

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Abstract

Subjects receiving treatment with ototoxic agents were evaluated concurrently with conventional and high-frequency (≥8 kHz) behavioral threshold measures and with ABR to click and to 8, 10, 12, and 14 kHz tone-burst stimuli. Behavioral threshold data revealed ototoxic change in 51 percent of ears evaluated. Of these ears demonstrating behavioral change, 90 percent revealed concurrent ABR changes. If only ABR monitoring with high-frequency tone-burst stimuli had been used, 87 percent of all ears showing behavioral change would have been identified. Three fourths of these would have been identified from wave V responses, with 87 percent identified from the two highest frequencies tested for each individual. This research suggests that behavioral change is reflected accurately in the ABR, that high-frequency tone bursts will identify a majority of initial ototoxic changes, and that monitoring hearing with high-frequency, tone-burst-evoked ABRs during treatment with potentially ototoxic agents is significantly more effective than click-evoked ABRs for early detection of ototoxicity.

Key Words: Aminoglycoside antibiotics, auditory brainstem response (ABR), auditory evoked potentials, cisplatinum, early detection, high-frequency audiometry, ototoxicity, serial monitoring

An estimated four million patients in the United States are treated with aminoglycoside antibiotics annually (Whelton, 1985). Aminoglycosides are responsible for three fourths of all ototoxicity caused by drugs (Govaerts et al, 1990). A chemotherapeutic agent, cis-dichlorodiammineplatinum (cisplatinum), is also well known to cause significant and permanent hearing loss in many individuals (Tange et al, 1985; Waters et al, 1991).

Ototoxic hearing loss typically begins with impairment of higher frequency thresholds with progression of damage into the lower frequency range (Tange et al, 1982; Bhattacharyya and Dayal, 1984; Barron and Daigneault, 1987; Huizing and DeGroot, 1987). This has been documented in human studies using behavioral conventional frequency (0.25–8 kHz) pure-tone serial monitoring, in which it was found that a majority of subjects demonstrating ototoxic side effects revealed initial threshold shifts at the highest frequencies tested (Fee, 1980; Fleming et al, 1985; Skinner et al, 1990). Behavioral serial monitoring at high frequencies (8–20 kHz) has been documented to detect ototoxicity earlier than with evaluation limited to the conventional frequency range (Holm et al, 1983; Fausti et al, 1984a, b; Tange et al, 1985; van der Hulst et al, 1988; Dreschler et al, 1989). Early detection provided by high-frequency hearing evaluation allows the health care provider to examine potential treatment alternatives prior to onset of hearing impairment which can affect communicative ability. Conversely, in the continued absence of evidence of the ototoxic...
process, more aggressive treatment options may be attempted without threat of communicatively handicapping hearing loss.

Obtaining reliable, valid behavioral hearing threshold responses requires the active cooperation and attention of a subject. Based on a 3-month survey at the Portland, Oregon Veterans Affairs Medical Center (PVAMC), it was estimated that 30 percent of hospitalized patients receiving treatment with aminoglycosides were unable to provide voluntary responses (Fausti et al, 1991b). A significant number of additional patients were able to provide responses, but were found to be unreliable. These unresponsive individuals may be more susceptible to communicatively handicapping hearing impairment than the individual able to provide necessary and timely subjective information (Whelton, 1985).

The auditory brainstem response (ABR) evoked by click stimuli has proven valuable as an objective auditory monitoring tool for patients unable to respond reliably to behavioral testing and has been demonstrated to be a reliable objective indicator of ototoxicity (Bernard et al, 1980; Guerit et al, 1981; Pick et al, 1985; Hall et al, 1986). Click stimuli, however, are broad-band signals, which provide limited information about auditory threshold. These stimuli evoke data that are representative primarily of the 2 to 4 kHz range of hearing (Gorga et al, 1985; Mitchell et al, 1989). Tone-burst ABR stimuli in the conventionally tested range (<6 kHz) of hearing have demonstrated greater frequency-specific sensitivity than clicks (Gorga et al, 1988; Fjermedal and Laukli, 1989; Purdy et al, 1989). However, because click and low-frequency tone-burst stimuli are expected to be most sensitive to ototoxic hearing loss in the conventional frequency range, their usefulness would be limited to the identification of hearing loss after progression into the range of hearing necessary for speech communication.

The ability to obtain reliable ABRs to frequency-specific (tone-burst) stimuli at 8 kHz and above has been demonstrated in normal-hearing persons (Gorga et al, 1987; Fausti et al, 1991a). Preliminary data from this laboratory have also shown that repeatable ABRs can be obtained from individuals with sensorineural hearing loss (unpublished data). The primary purpose of this study was to determine the clinical usefulness of ABRs evoked by high-frequency tone-burst stimuli (8, 10, 12, and 14 kHz) as an early detector of hearing loss caused by aminoglycoside antibiotic and cisplatinum treatment in responsive patients. To this end, the relationship between behavioral and objective auditory evaluation results was examined. The ultimate goal of this research is to provide a clinical tool that can be used to accurately monitor hearing function in unresponsive patients who cannot be tested with traditional behavioral methods.

METHOD AND MATERIALS

Subjects

Entry criteria for all subjects included: (1) no active or recent history of middle ear pathology, and no history of retrocochlear or Ménière’s pathologies; (2) baseline behavioral hearing thresholds ≤100 dB SPL at 10 and 11.2 kHz in at least one ear; (3) reliable responses to conventional and high-frequency pure-tone audiometry based upon ability to obtain intrasession repeated thresholds within ±5 dB; (4) acquisition of baseline hearing thresholds prior to treatment or within 72 hours after initial treatment dose for aminoglycoside-treated patients (amikacin, gentamicin, tobramycin) and within 1 week prior to 24 hours following initial dose for cisplatinum-treated patients; (5) a minimum of 4 days of drug therapy for aminoglycoside-treated patients or at least one chemotherapeutic dose for cisplatinum-treated patients; and (6) reliability of click- and tone-burst-evoked ABRs as determined by intrasession replicability within ±0.3 msec for waves I and V. Fifty-three hospitalized male subjects with a mean age of 57 years met the study inclusion criteria and agreed to participate.

Instrumentation

All testing was completed in an Acoustic Systems 19701A, RF-shielded sound-treated booth. Behavioral pure-tone testing was conducted with a Virtual 320 audiometer. In the frequency range below 8 kHz, TDH-50P earphones in MX-41/AR cushions were used. Koss Pro/4X Plus earphones, modified as described in Fausti et al (1990), were used for frequencies at and above 8 kHz. Tympanometry and contralateral acoustic reflexes were performed with a Virtual 310 aural acoustic-immittance system.

All ABR signal averaging and presentation of click stimuli were performed with a Bio-logic Traveler portable signal averager. Earphones utilized for click stimuli were TDH-39P, while
those used for all tone-burst stimuli were the modified Koss Pro/4X Plus. Tone-burst stimuli at 8, 10, 12, and 14 kHz were produced by a portable stimulus generator described in detail in Fausti et al (1992). One-decibel step attenuation, used in behavioral threshold determinations for tone-burst stimuli, was attained with insertion of a Hewlett-Packard 350D attenuator.

**Calibration**

All instrumentation was calibrated daily prior to testing. Pure tones from 0.25 to 6 kHz were calibrated in accordance with ANSI standards (1989). Pure tones from 8 to 20 kHz were calibrated as described in Fausti et al (1979b). Click and tone-burst stimuli were calibrated as described in Fausti et al (1991a). The acoustic-immittance system was internally calibrated according to manufacturer's guidelines prior to each use, and was electroacoustically calibrated by a manufacturer's representative every 3 to 6 months.

**Procedures**

All behavioral pure-tone, click, and tone-burst thresholds were obtained using the clinically accepted ascending-descending modified Hughson-Westlake technique of Carhart and Jerger (1959). For clicks and tone bursts, 1000 stimuli were presented during each ABR run. Intrasession runs were replicated for each stimulus condition. A two-channel electrode montage was utilized with the electrode amplifier input ground placement at the forehead; noninverting at the vertex; channel 1 inverting on the right mastoid; and channel 2 inverting on the left mastoid. Ipsilateral and contralateral recordings were gathered simultaneously for all test conditions. Absolute impedance did not exceed 2 kΩ and the interelectrode impedance differences were at or below 1 kΩ. Bioamplifier filter settings were 100 to 1500 Hz, and the artifact rejection mode was enabled.

**Baseline Testing**

Initial session baseline evaluation included immittance testing (tympanometry at 226 and 678 Hz, and contralateral acoustic reflexes at 0.5, 1, 2, and 4 kHz), pure-tone air-conduction testing (0.25–20 kHz), behavioral thresholds to click and tone-burst stimuli, and ABRs for clicks and all tone-burst frequencies (8, 10, 12, and 14 kHz). ABR intensity levels were set at 60 dB SL, based upon the behavioral thresholds to click and tone-burst stimuli established at baseline. Baseline presentation levels were held constant for all subsequent evaluations. Sensation level (SL) was used rather than a fixed peSPL due to large differences in high-frequency hearing thresholds typically seen for even normal-hearing individuals up to 30 years of age (Schechter et al, 1986). The target population, predominantly noise-exposed hospitalized veteran patients averaging nearly 60 years of age, will display even larger variations. A supra-threshold level of 60 dB was selected to ensure the most scorable waveforms and the best possible retest reliability. When 60 dB SL presentations were not attainable due to poorer hearing thresholds, a maximum output level of 120 dB peSPL was presented. Although it is recognized that threshold measures may provide a more sensitive indicator of change, ABR thresholds were not obtained because of the considerable time involved in this process. Ill patients receiving ototoxic agents for potentially life-threatening pathologies must be tested in as little time as possible so as not to interfere with their treatment, exacerbate their condition, or cause them unnecessary discomfort.

**Monitoring during Treatment**

After baseline, pure-tone thresholds (0.25–20 kHz) and ABRs at baseline levels were collected from aminoglycoside-treated subjects every 2 to 3 days during treatment. Cisplatinum-treated subjects were evaluated prior to each dose. A minimum of three serial audiograms and ABRs was required for inclusion in data analysis.

**Follow-Up Tests**

For aminoglycoside-treated subjects, follow-up evaluations occurred immediately after termination of treatment, and, whenever possible, at 1- and 6-months post treatment. Cisplatinum-treated subjects were also followed at 1- and 6-months post treatment when possible.

**Wave Identification**

Wave identification techniques used with standard ABR click stimuli (Chiappa et al, 1979; Picton et al, 1988) were employed as a guideline for peak picking with high-frequency, tone-burst stimuli. To facilitate peak identifi-
cation, ipsilateral waveforms were compared to contralateral waveforms from the same run and added ipsilateral waveforms from replicated runs for each of the stimulus parameters. Initial observations revealed many missing data points for wave III. Therefore, absolute latencies were measured for only waves I and V.

**Ototoxic Change Criteria**

Each subject served as his own control, and change was computed in relation to baseline measures.

**Behavioral**

Behavioral criteria for change in hearing were operationally defined as: (1) ≥20 dB change at any single frequency; (2) ≥10 dB change at any two consecutively tested frequencies; or (3) loss of response at any three consecutively tested frequencies (Fausti et al, 1979a, 1984a; Rappaport et al, 1985). Pure-tone behavioral threshold changes were considered the standard of reference for comparison with ABR latency changes. For purposes of this study, behavioral high frequencies begin at 8 kHz, to correspond with the 8 kHz tone burst, which is classified as a high frequency. Thus, the conventional frequency range is defined as being below 8 kHz.

**ABR**

In a study demonstrating intersession reliability of high-frequency tone bursts in normal-hearing individuals, Fausti et al (1991b) presented cumulative percentage data of subjects as a function of intersession latency differences. For a given wave and stimulus, it could be determined what percentage of the difference scores were greater than or less than a given value. The intrasubject, intersession latency differences were similar for waves I and V. Thus, similar criteria could be used to detect a change in latency for each wave. Based on these normative test-retest and latency-intensity data and on clinical observation, a change in click or tone-burst ABR latencies was operationally defined as: (1) a latency shift greater than 0.3 msec at wave I or wave V; or (2) a scorable response degrading to an unscorable response.

**RESULTS**

Of 53 subjects entered into this study, 34 subjects (61 ears) completed study requirements for being monitored both behaviorally and with ABR. Thirty-one of the 61 ears (50.8%) demonstrated behavioral pure-tone changes. Figure 1 displays the mean baseline audiogram, with one-standard deviation bars and percentage of ears responding at each frequency.

Table 1* Ototoxicity Detectability: Behavioral versus Objective

<table>
<thead>
<tr>
<th></th>
<th>Behavioral</th>
<th>Objective</th>
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<tbody>
<tr>
<td>High Frequencies Only</td>
<td>23</td>
<td>High Frequency TB Only</td>
</tr>
<tr>
<td>High Frequency/Conventional</td>
<td>5</td>
<td>High Frequency TB/Clicks</td>
</tr>
<tr>
<td>Conventions Only</td>
<td>3</td>
<td>Clicks Only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No ABR Change</td>
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*N = 31.

TB = tone-burst stimuli.
burst and click stimuli. Behaviorally, 23 ears showed initial change only in the high frequencies (>8 kHz), 3 ears showed initial change only in the conventional frequencies (≤6 kHz) and 5 ears showed initial behavioral change in both high and conventional frequencies. Of these 31 ears demonstrating behavioral changes, 28 (90.3%) revealed concurrent ABR latency/morphology changes to click and/or high frequency tone-burst stimuli. Of the ABR-change ears, 20 showed initial changes in high-frequency, tone-burst-evoked responses, only 1 ear showed change solely in the click-evoked ABR and 7 showed initial changes in both click-evoked and high-frequency, tone-burst-evoked responses. Thus, high-frequency, tone-burst-evoked ABRs concurrently identified 27 of the 31 ears (87.1%) demonstrating behavioral change. Furthermore, if only ABR had been utilized, 27 of the 28 ears identified with this method would have been detected using only high-frequency, tone-burst stimuli (96.4%), as compared to 8 of 28 ears (28.6%) detected from click stimuli (Fig. 2).

Because of a paucity of wave I responses, the following analysis deals with only wave V. Analysis of wave V data revealed that 23 of the 28 ABR change ears (82.1%) were identified solely from wave V responses to high-frequency tone bursts. Furthermore, 11 of the 23 wave V changes were seen to occur in the highest ABR frequency tested for each subject. When the two highest test frequencies were examined, 20 of 23 (86.9%) wave V changes were detected. Of the 28 ears demonstrating ABR change, 17 (60.7%) revealed response waveform morphologies in which wave V at either of the two highest frequencies tested for each individual was degraded from initially scorable to no response.

A group of 12 subjects (18 ears) who did not meet study entry criterion for hearing thresholds ≤100 dB SPL at 11.2 kHz were analyzed separately. Our interest with these subjects was in determining how poorer hearing subjects might compare to the better hearing subjects in the study sample. Nine of these 18 ears revealed behavioral pure-tone threshold changes. All 9 behavioral change ears demonstrated concurrent ABR changes. Five of these ears showed ABR wave V changes to high-frequency, tone-burst stimuli at the highest frequency evaluated for each subject. This number increased to 7 for the two highest frequencies. Three had scorable baseline ABRs which declined to unscorable responses.

The following case example demonstrates a concurrent change in behavioral thresholds and ABR. A 62-year-old male was administered two doses of cisplatinum, and a 6-day treatment course of gentamicin. He was evaluated five times with both behavioral and ABR tests. Significant threshold changes were seen bilaterally. Detected initially at frequencies above 10 kHz, the loss progressed until all frequencies above 2 kHz for both ears were affected. Figure 3 shows baseline and final behavioral test results for the right ear. ABRs corresponded with behavioral tests, in that significant high-frequency threshold changes were mirrored by latency changes in the high-frequency, tone-

**Figure 2** Percentage of ears that demonstrated ototoxic hearing change with ABRs to the two types of stimuli utilized.

**Figure 3** Behavioral threshold audiogram showing base-line and final evaluations for the right ear of a 62-year-old male who received two cisplatinum treatments and a 6-day course of treatment with gentamicin.
burst-evoked ABR. The baseline and final ABRs to click stimuli are seen in Figure 4 (Top). Note the minimal shift in latency in spite of the significant behavioral threshold shifts above 2 kHz. Baseline and final ABRs to 12 kHz tone-burst stimuli are shown in Figure 4 (Bottom). Note the scorable wave V at baseline, with no identifiable response on the final waveform. This case demonstrates the sensitivity of the high-frequency, tone-burst-evoked ABR, and the limitation of click-evoked ABR in early detection of ototoxicity.

**DISCUSSION**

Behavioral monitoring of hearing thresholds during administration of potentially ototoxic drugs has shown that ototoxicity begins in the highest frequencies of hearing with progression into lower frequencies. Therefore, for early detection of hearing loss, this high-frequency region should be serially monitored during periods of treatment with such drugs. Awareness of the status of high-frequency hearing during treatment enables health care providers to make more informed treatment decisions with regard to the presence or absence of ototoxicity.

Characteristicly, it is the most seriously ill patients, and hence those at higher risk for side effects of aminoglycosides, who are typically removed from the analysis of ototoxicity. (Whelton, 1985).

Common to most medical center care facilities is the large number of hospitalized patients receiving potentially ototoxic medications who cannot undergo additional, voluntary testing. Additionally, lengthy auditory test procedures often conflict with medical treatment procedures. The large number of at-risk patients is increased when, in addition to patients who are unconscious, or comatose, those who are simply too ill to provide reliable responses over time needed for monitoring are included. These untestable patients point out the obvious need for an objective hearing measurement technique capable of providing auditory information adequate enough to allow accurate judgment with regard to the presence or absence of ototoxicity.

This study was conducted for the purpose of comparing serial ABRs evoked by clicks and high-frequency-specific tone bursts, obtained during ototoxic drug treatment, with concurrently obtained behavioral auditory thresholds. Because both unilateral and bilateral changes were observed, analyses were conducted on ears rather than subjects. A behavioral hearing change was seen in 51 percent of ears. This high rate of incidence is, in all probability, a reflection of the expanded frequency range for auditory monitoring (0.25–20 kHz) and of the type and extent of preexisting hearing loss seen in this subject sample. Of those ears demonstrating behavioral threshold changes, a significant majority (90%) demonstrated concurrent ABR changes.

Although ABRs to click stimuli detected change in 8 of the 31 ears in which behavioral changes were initially observed, all but 1 of these ears were also identified with high-frequency, tone-burst-evoked ABR. Thus, only about 3 percent of the entire hearing change group was detected solely with click-evoked ABRs. High-frequency, tone-burst-evoked ABRs, on the other hand, were successful in
identifying over 87 percent of ears demonstrating behavioral change.

It is well known that definition of waveform declines as threshold is approached, with wave V the last to disappear. Further analysis revealed that, if only wave V data had been considered, nearly three fourths of all change ears would have been detected from high-frequency, tone-burst-evoked ABRs, with the majority of these ears (87%) identified from only the two highest frequencies tested.

Of the 28 ears that demonstrated ABR change, 17 revealed initially scorable wave V responses, which degraded to unscorable. The baseline hearing sensitivity of the subjects in this study tended to place ABRs to high-frequency, tone-burst stimuli closer to threshold. Additional loss of hearing sensitivity from ototoxicity under this condition could account for the large percentage of responses observed to be scorable at baseline, with subsequent waveform degradation that precluded scoring. These ABR changes represent a major degradation of wave morphology, which mutes any controversy regarding the absolute change in wave latency that must be observed before being classified as an ototoxic change.

A group of subjects with ears failing to meet study inclusion criteria for baseline thresholds were also evaluated both behaviorally and objectively. The same characteristic ototoxic change phenomena seen in the better hearing group were observed in this group. These poorer hearing subjects showed that the ABR to high-frequency tone bursts does not appear to lose significant effectiveness for early ototoxic detection with diminished hearing sensitivity in the high-frequency range.

Additional observation showed that small (<20 dB) behavioral pure-tone changes were most often not reflected in the ABR when the original response was robust. That is, when ABRs were highly definable, as was most often the case in subjects with good high-frequency hearing thresholds, greater pure-tone changes were required for shifts in absolute latency to be observed. However, in some cases the morphology (including amplitude) of the response was observed to change while wave latency remained stable. These waveform morphology changes may merit further investigation.

SUMMARY

Data from this study revealed that high-frequency tone-burst-evoked ABRs identified a high percentage of initial ototoxic change, typically mirroring the loss of hearing seen behaviorally. The two highest ABR tone-burst frequencies monitored for each individual were generally the most indicative of initial objective change. Of waves I and V, wave V was shown to be the best indicator of initial change. The most frequently observed change was from a scorable to an unscorable response. The ABR evoked by high-frequency tone bursts was demonstrated to be superior to the click-evoked ABR in early detection of ototoxicity.

This research was conducted with responsive subjects who were able to provide reliable behavioral and ABR data gathered at the same time for comparison. The ultimate goal, however, is to provide auditory monitoring for all possible subjects, including those who are unreliable or unresponsive. Based on the observed relationship between behavioral and ABR changes, this technique shows considerable promise.

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