High-frequency testing techniques and instrumentation for early detection of ototoxicity

Stephen A. Fausti, PhD; Richard H. Frey, BS; James A. Henry, MS; Deanna J. Olson, MS; Heidi I. Schaffer, MA
Department of Veterans Affairs Medical Center, Portland, OR 97207; Department of Otolaryngology, Oregon Health Sciences University, Portland, OR 97207

Abstract—Veteran patients with certain types of infections and cancers are routinely treated with therapeutic agents having ototoxic potential, thus threatening loss of hearing sensitivity which preexists in the majority of these patients. To prevent communication deficits requiring intervention, this laboratory is developing instrumentation and techniques for early detection of ototoxicity. For this study, conventional (< 8 kHz) and high-frequency (≥ 8 kHz) hearing thresholds were monitored behaviorally in hospitalized veterans receiving treatment with ototoxic drugs. Data analysis revealed that monitoring only the high-frequency range would have identified 67% of ears showing change. A five-frequency range of hearing, specific to each individual, was identified for its high sensitivity to early ototoxic change. Monitoring of only these five frequencies in each patient would have identified 82% of ears that showed behavioral change. Auditory brainstem responses (ABR) were obtained in a subgroup using clicks and high-frequency (8–14 kHz) tone bursts. ABR latency/morphology changes were observed in 95% of ears demonstrating behavioral change. High-frequency tone-burst-evoked ABRs alone would have identified 93% of initial changes. Monitoring of high-frequency audition using these techniques shows promise for early detection of ototoxicity with potential for prevention of hearing loss in frequencies essential for verbal communication.

Key words: early detection, high frequency, instrumentation, monitoring, ototoxicity, prevention, technique.

INTRODUCTION

As a major cause of communication disorders, hearing loss has a serious impact on the general population. Because of its importance to communication, hearing loss can profoundly affect the ability of a person to function socially and vocationally. More than 28 million individuals in the United States have hearing impairment (1). In men over the age of 55, the prevalence of reduced high-frequency hearing sensitivity has been estimated at 55 percent (2). A majority of the population served by the VA Medical Center system falls within this age group. In fact, the largest group of veterans with service-connected disabilities consists of those with hearing loss.

Because of their high probability of preexisting hearing loss, a particularly significant issue for veteran patients is ototoxicity from treatment with therapeutic drugs such as aminoglycoside antibiotics (AMG) and the chemotherapeutic agent cisplatin (CDDP). Exacerbation of hearing loss by ototoxic
drugs can be functionally devastating to the veteran if speech recognition ability is impaired. Furthermore, the ability of the VA to treat individuals in programs such as speech and language pathology, alcohol and drug dependency, blind rehabilitation, and post-traumatic stress disorders can be significantly affected by hearing loss. The patient is best served if rehabilitation is obviated by successful prevention of the handicapping condition.

Animal studies have suggested that hearing loss from ototoxicity begins in the highest audible frequencies (3,4,5). Human auditory testing programs monitoring drug-induced hearing loss with conventional audiometers (≤8 kHz) also have shown that the highest frequencies evaluated were the first to be affected (6,7). An initial ototoxic symptom often reported by patients is increased difficulty in understanding speech in a noisy environment. When a communication deficit becomes subjectively apparent, it is likely that significant hearing loss below 4,000 Hz has been sustained. In medical centers where patients receiving ototoxic drugs are monitored for hearing changes, the procedure usually involves conventional audiometry (≤8 kHz). However, when detected with this procedure, hearing loss will have progressed either into or near the range where speech communication is affected. Since hearing loss from most ototoxic agents appears to begin in the highest audible frequencies with progression to lower frequencies, monitoring of high-frequency (≥8 kHz) thresholds should detect hearing change earlier than testing only with lower, conventional frequencies.

Fausti, et al. (8) evaluated available instrumentation for use in high-frequency (≥8 kHz) testing, and found insufficient maximum power output, poor signal-to-noise (S/N) ratios and difficulty in calibrating transducers. A component high-frequency evaluation system was developed which provided the necessary outputs and high S/N ratios required for the study of high-frequency thresholds. This system was demonstrated to be reliable (9) and valid (10), and was used to conduct a series of studies evaluating the side effects on high-frequency hearing from ototoxic drug administration (11,12,13,14). Based on the development of the laboratory high-frequency evaluation system, a high-frequency audiometer was subsequently commercially manufactured. The 1980s saw the emergence of three additional high-frequency audiometers in the United States, thus providing instrumentation capable of full-frequency-range behavioral ototoxic monitoring.

It is common that medical centers have a significant number of hospitalized patients receiving potentially ototoxic medications who cannot be evaluated by behavioral audiometric techniques. It was estimated that more than 30 percent of veteran hospitalized patients administered potentially ototoxic drugs at the VA Medical Center, Portland, Oregon, were unable to be tested by behavioral auditory evaluation methods (15). These unresponsive patients typically do not receive any auditory monitoring for detection of ototoxic effects. In addition to unresponsive patients, many patients can respond to behavioral testing, but due to their illness may provide unreliable results over time. Thus, there is a need for an objective method of monitoring hearing in unresponsive patients to provide information as early as possible regarding hearing change (or absence of change).

Evoked otoacoustic emissions (EOAE) may have potential as an objective technique for ototoxic monitoring (16). However, the usefulness of current EOAE instrumentation and techniques is restricted to regions of good hearing sensitivity. For ototoxic monitoring and early detection of hearing change, high-frequency (≥8 kHz) evaluation is desired, and sensitivity in this range is reduced even in the normal-hearing patient. For the eventual application of on-the-ward monitoring for ototoxicity, we have chosen the more widely used, noninvasive auditory brainstem response (ABR) technique.

The 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 potential objective indicator of ototoxicity (17,18,19,20). However, click stimuli, as well as traditional tonebursts (<8 kHz), detect changes in hearing sensitivity in the conventional-frequency range. Tonebursts at frequencies of 8 kHz and above could be expected to objectively detect initial ototoxicity if reliable ABRs could be obtained with these stimuli.

Early studies in this laboratory demonstrated the feasibility of high-frequency toneburst ABR using a rack-mounted laboratory system that presents high-frequency tonebursts at 8, 10, 12, and 14 kHz (8,21). Later studies using this system analyzed the effects of rise time and center fre-
quency on the ABR (22) and demonstrated the reliability of ABRs to these high-frequency toneburst stimuli in normal-hearing subjects (23). This high-frequency toneburst system was designed for evaluating responsive subjects in the laboratory environment. Testing unresponsive, nonambulatory patients, however, required the development of a portable system, described in Fausti, et al. (15), which could be transported to a patient’s bedside. Validity of measurements collected on the portable system was demonstrated by confirming that responses were equivalent to those elicited by the laboratory system (24).

Any means of reducing or preventing hearing loss is clearly desirable. To minimize or prevent ototoxicity, this laboratory has focused on the development of instrumentation and techniques for high-frequency (8–20 kHz) hearing threshold evaluation. Development has systematically branched in two directions, the first involving high-frequency puretone audiometric techniques, and the second being objective techniques designed for subjects who cannot respond to behavioral methods. Development of both of these methods would enable the majority of patients being treated with potentially ototoxic agents to receive efficacious auditory monitoring during the course of their treatment. Results are reported from a midpoint of an ongoing study of hospitalized veterans receiving ototoxic drug treatment. These patients were prospectively monitored behaviorally in both conventional- and high-frequency ranges for the purpose of identifying frequency regions most susceptible to threshold change as a result of treatment. A subgroup of patients also received click- and high-frequency toneburst-evoked ABR monitoring to look for concurrent changes between latency/morphology of waveforms and puretone thresholds.

METHODS

Subjects
Subject inclusion criteria included: (a) no active aural pathology; (b) ≥4 days of treatment for AMG, or ≥1 dose for CDDP; (c) baseline audiogram obtained within 72 hours after the initial dose of AMG, or within the period of 1 week prior to 24 hours after the initial dose of CDDP; and, (d) behavioral baseline thresholds ≤100 dB SPL at 10

and 11.2 kHz. These criteria were met by 83 patients (averaging 56 years of age) who were included as subjects in this study. Of these subjects, a total of 131 ears have been included in puretone data analyses to date, including 94 AMG-treated ears and 37 CDDP-treated ears.

Instrumentation
For evaluation of puretone thresholds (0.25–20 kHz), the Virtual Corporation Model 320 (V320) audiometer was used. Reliability and validity of subject responses to high-frequency stimuli using this instrument have been documented (25). Earphones used when testing conventional frequencies were TDH-50P in MX-41/AR cushions. Modified Koss Pro/4X Plus earphones were used for high-frequency testing (25). All instrumentation was calibrated daily prior to testing. Puretones from 0.25 to 8 kHz were calibrated in accordance with ANSI standards (26). Puretones from 9 to 20 kHz were calibrated as described in Fausti, et al. (8). Tympanometry and acoustic reflex testing were done with a Virtual Corporation Model 310 aural acoustic-immittance system.

ABR signal averaging and presentation of click stimuli were performed with a Bio-logic Traveler. Earphones utilized with click stimuli were TDH-39P, while those used for all toneburst stimuli were the modified Koss Pro/4X Plus. Toneburst stimuli at 8, 10, 12, and 14 kHz were produced by the portable stimulus generator designed and developed in this lab (15). Tonebursts utilized were ramp-windowed, with 0.2 msec rise-fall times and 1.6 msec plateaus. Click and toneburst stimuli were calibrated as described in Fausti, et al. (22).

Procedures
Baseline evaluation for all subjects included immittance testing (tympanometry at 226 and 678 Hz, and contralateral acoustic reflexes at 0.5, 1, 2, and 4 kHz), and behavioral thresholds to air-conducted puretones (0.25, 0.5, 1, 2, 3, 4, 6, 8, 9, 10, 11.2, 12.5, 14, 15, 16, 18, and 20 kHz). The modified Hughson-Westlake technique of Carhart and Jerger (27) was used to obtain all behavioral thresholds. Following baseline evaluation, puretone thresholds (0.25–20 kHz) were obtained from AMG-treated subjects every 2–3 days during treatment. CDDP-treated subjects were evaluated prior to each dose. Follow-up evaluations occurred immediately
after termination of treatment, and at 1 month and 6 months post-treatment.

The subgroup evaluated with ABR received ABR baseline testing and monitoring on the same schedule as the behaviorally tested subjects. ABRs were obtained to clicks and to tonebursts of 8, 10, 12, and 14 kHz. For clicks and each toneburst stimulus condition, 1,000 stimuli were presented during each ABR averaging run, and all runs were replicated. A two-channel electrode montage was utilized with ground placement on the forehead, noninverting on the vertex, channel-1 inverting on the right mastoid, and channel-2 inverting on the left mastoid. Ipsilateral and contralateral recordings were collected simultaneously. Absolute impedance for all electrodes was ≤2 kΩ, and interelectrode impedance differences were ≤1 kΩ. Bioamplifier filter settings were 100-1500 Hz, and the artifact rejection mode was enabled.

Because of large differences in high-frequency hearing thresholds in the targeted veteran patients, a suprathreshold level of 60 dB sensation level (SL) was selected for ABR testing rather than a fixed peak-equivalent SPL (peSPL). Levels were based upon behavioral thresholds to click and toneburst stimuli established at baseline and were held constant for all subsequent evaluations. When a 60 dB SL presentation level was not attainable because of poor hearing thresholds, an output level of 125 dB peSPL was presented. Objective thresholds could not be determined because of the excessive time involved in obtaining ABR latency-intensity functions. Ill patients must be tested in as little time as possible so as not to exacerbate their condition, cause them unnecessary discomfort or interfere with their treatment.

Guidelines for wave identification in ABRs to high-frequency toneburst stimuli were based on techniques used with click stimuli (28,29). Peak identification was facilitated by comparing ipsilateral waveforms to simultaneously collected contralateral waveforms and to added ipsilateral waveforms from replicated runs.

**Ototoxic Change Criteria**

Ototoxic change was computed in relation to baseline measures, with each subject serving as his own control. Behavioral criteria for change in hearing were operationally defined as: (a) ≥20 dB change at any single frequency; (b) ≥10 dB change at any two consecutively tested frequencies; or, (c) loss of response at any three consecutively tested frequencies.

Puretone behavioral threshold changes were the standard of reference for comparison with ABR latency/morphology changes. Criteria for defining change in ABR were established from previous studies of latency-intensity (L-I) functions (30) and intersession reliability (23) of ABRs to high-frequency tonebursts in normal-hearing individuals. Based on these normative values, a change in click or toneburst ABR latencies as compared to baseline was operationally defined as: (a) a latency shift greater than 0.3 msec at wave I or wave V or (b) a scorable response degrading to an unscorable response.

**RESULTS**

Of the 131 study ears, 91 showed behavioral change according to our operational definition of ototoxicity. Ears that demonstrated ototoxic change were analyzed to determine whether initial change was detected in the high-frequency range, conventional-frequency range, or in both ranges concurrently. Of all change ears, 52 percent were first detected in the high-frequency range only, 15 percent in both frequency ranges concurrently, and 33 percent in the conventional-frequency range only (Figure 1). Thus, 67 percent of all ears demonstrating initial ototoxic change were detected by high-frequency evaluation as compared to 48 percent by conventional-frequency evaluation.

It was observed that baseline high-frequency thresholds greater than 100 dB SPL showed fewer changes throughout drug treatment than thresholds at or below 100 dB SPL. This led to data analyses focusing on a frequency range of hearing where ototoxicity was most likely to initially appear. Considering the unique hearing threshold configuration of each patient, frequencies with thresholds at or below 100 dB SPL were examined for each test ear. The result was identification of a frequency range, unique to each individual, within which the initial detection of ototoxicity was most probable. This range was identified as five consecutive frequencies from the high-frequency range (i.e., at or above 8 kHz).
Figure 1.
Frequency-range categorization of initial puretone change for ears demonstrating ototoxicity: High (high-frequency range only, i.e., ≥8 kHz), Both (high- and conventional-frequency ranges concurrently), and Low (conventional-frequency range only, i.e., ≤8 kHz).

Figure 2.
Detection of initial hearing change in relationship to the five-frequency range. If only the frequencies within the five-frequency range had been tested, 82 percent of ears that changed would have been identified.

Data from change ears were analyzed to determine what the detection rate would have been if patients had been tested only in their five-frequency range. Initial change was seen to occur only in this restricted range in 58 percent of change ears. Change was seen concurrently in both the five-frequency range and in lower frequencies in 24 percent of the ears, with only 18 percent of all the change ears demonstrating initial change solely in the frequencies below the five-frequency range. Thus, if these patients had been monitored for auditory thresholds within their five-frequency range only, 82 percent of ears showing change would have been detected when they first demonstrated ototoxicity (Figure 2).

From the subgroup of responsive subjects monitored both behaviorally and objectively, 29 ears showed behavioral change. Figure 3 displays frequency ranges where initial changes were seen both behaviorally and objectively for all 29 ears. Initial behavioral puretone change is indicated on the left side of the figure and includes High (high frequencies only, i.e., ≥8 kHz), Both (high and conventional frequencies concurrently), and Low (conventional frequencies only). Listed at the top of the graph are frequency ranges where initial change was detected objectively, including HF TB (high-frequency tonebursts only), Both (high-frequency

Figure 3.
Grid analysis of frequency ranges of initial detection of ototoxicity in ears concurrently monitored behaviorally and objectively. (Top of graph: HF TB = high-frequency toneburst; Both = HF TB and clicks; None = no change detected. Left side of graph: High = high-frequency range; Both = high- and conventional-frequency ranges; Low = conventional-frequency range.)
tonebursts and clicks concurrently), Clicks (clicks only), and None (no change detected objectively). It can be seen that of the 21 ears that changed behaviorally in the high-frequency range only, 20 were also seen to change in response to high-frequency tonebursts, and 1 ear changed in response to clicks. Six ears changed behaviorally in both the high and conventional frequency ranges concurrently, of which three were detected solely with high-frequency tonebursts and three were detected with high-frequency tonebursts and clicks concurrently. Two ears changed behaviorally in the conventional range only, of which one was detected objectively with high-frequency tonebursts and clicks concurrently, and one was not detected objectively. If these 29 ears had been monitored only with high-frequency toneburst ABR, 27 ears (93 percent) would have been detected according to our ABR change criteria.

Subsequent data analysis of ABR results has been performed to determine differential wave sensitivity to initial change. Of the individual response waves (I, III, and V), wave V demonstrated the most persistence and provided the highest percentage of detection with respect to ototoxic change. Wave V responses to high-frequency tonebursts met the criteria for change in 82 percent of those ears that changed objectively. Also, 48 percent of wave V changes occurred in the highest ABR frequency at which a response was obtained for each subject, and 87 percent of changes were seen in the two highest frequencies. Finally, at either of the two highest response frequencies for each individual, in 61 percent of change ears wave V was degraded from initially scorable to a nonscorable trace.

DISCUSSION

The risk of hearing loss in an individual as a consequence of ototoxic drug treatment is essentially unknown. The ototoxicity literature is highly variable with respect to reports of incidence and monitoring methodology. Most studies have limited hearing threshold evaluation to the conventional-frequency range. However, once hearing loss is detected with this conventional method, damage has already invaded the frequency range that can affect communication ability. In early studies, data collection methods were either unreported or widely variable, and the definition for ototoxic change was inconsistent. Standards, or even agreed-upon guidelines, for monitoring ototoxic effects still do not exist.

Since ototoxic hearing loss seems to begin in the high frequencies, identification of initial loss in the high-frequency region should give health care providers an early warning of ototoxicity and allow the appraisal of potential treatment alternatives before the loss progresses to include frequencies critical for verbal communication. Unfortunately, biases exist against audiometric monitoring of patients receiving treatment with potentially ototoxic drugs. A common misconception is that ongoing monitoring of hearing during treatment is inconsequential if the patient's chance of survival is considered minimal. For example, patients administered CDDP are often considered terminal cases, but the efficacy of CDDP treatment has increased their survival rate (31,32), arguing for the need to protect their hearing. Another misconception is that high-frequency (8-20 kHz) thresholds are unobtainable in patients with preexisting hearing loss, especially those patients over 40 years of age. As was shown by our sample of middle-aged males, high-frequency thresholds are obtainable in patients with preexisting hearing loss.

In continuing investigations regarding the efficacy of strategies for early detection of ototoxicity, this laboratory has attempted to examine and define those frequencies most susceptible to the ototoxic action of AMG and CDDP. Data reported in this study have been analyzed at an interim point of our ongoing research. This data pool is being continually expanded, as the need exists for further continuing research to obtain a larger database from which a more thorough analysis can be made. This will facilitate development of instrumentation and testing techniques to monitor the most sensitive frequency regions of hearing.

At the time of this data analysis, 131 ears were behaviorally monitored for ototoxicity, of which 91 showed a loss of hearing meeting our criteria. Collection of thresholds from 0.25 to 20 kHz during baseline and all monitoring allowed a retrospective comparison of three behavioral monitoring protocols (shortened from evaluating all frequencies from 0.25 to 20 kHz) for efficacy in early detection of ototoxicity: (a) high frequencies only, (b) conventional frequencies only, and (c) five-frequency range. If only the high frequencies had been
monitored in these patients, 67 percent of changes would have been identified when change first took place. This compares to 48 percent of changes that would have been identified using conventional-frequency audiometry on the same schedule. Analysis of the five-frequency range, specific to each individual's unique hearing threshold configuration, revealed that, had only these frequencies been monitored, 82 percent of all initial changes would have been detected. These results are beginning to clarify methodology for monitoring the hearing in these patients when testing time is a factor. Monitoring all frequencies from 0.25 to 20 kHz is a lengthy procedure that exceeds the abilities of many patients to provide reliable responses, and thus shortened protocols are essential for these patients.

In a hospital setting, there still remains a large number of patients unable to respond to any type of behavioral test, including patients who are unconscious or comatose and those who are simply too ill to provide reliable responses over the time needed for monitoring. These behaviorally unresponsive individuals may be even more susceptible to communicatively handicapping hearing impairment than persons able to provide subjective information (33). The need to prevent hearing loss in these unresponsive patients warrants the development of instrumentation and techniques to monitor their hearing during treatment with potentially ototoxic agents.

In the subgroup of patients who were monitored behaviorally and objectively, high-frequency toneburst-evoked ABRs were successful in identifying over 90 percent of all ears demonstrating behavioral change. Further data analysis revealed some notable points: the two highest ABR toneburst frequencies monitored for each individual were generally the most indicative of initial objective change; wave III responses were sparse, and 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; and ABRs evoked by high-frequency tonebursts were demonstrated to be clearly superior to click-evoked ABRs in early detection of ototoxicity. These results are presented as preliminary findings toward the development of a clinical tool to objectively monitor patients receiving potentially ototoxic medication. Based on the observed relationship between behavioral and ABR changes, this technique shows considerable promise. There is evidence that high-frequency evaluation is an early detector of ototoxicity, and that the high-frequency toneburst-evoked ABR method can be a valuable tool in early ototoxic detection with heretofore difficult-to-test subjects.

As with behavioral testing, the time involved in auditory monitoring with evoked potentials is a concern with seriously ill patients. To obtain repeated ABR latency-intensity functions with tonebursts at multiple frequencies and intensities, at least 1 hour of averaging time is required to evaluate a single ear. To shorten testing time, other stimuli for evoking the ABR at high frequencies are currently being examined, including a high-frequency click that would stimulate an entire range of frequencies within the high-frequency range of hearing, and multiple frequency and intensity toneburst stimuli delivered in a single pulse train (34). The technique utilizing pulse trains has received preliminary investigation in this laboratory. This technique uses the concept that an auditory stimulus produces a refractory area which has dimensions in time, frequency, and intensity. If the refractory areas of successive stimuli overlap, the response will be adapted. Conversely, if successive stimuli are presented outside the refractory area of preceding stimuli, adaptation can be avoided.

A multiple-frequency stimulus-train generator was designed and fabricated to digitally synthesize stimulus trains. Stimulus trains containing four interleaved tonebursts (8, 10, 12, and 14 kHz) have been utilized to evoke repeatable ABRs without waveform degradation as compared to single frequency toneburst presentations. This methodology is potentially clinically useful in routine ABR testing, and especially in situations where more rapid frequency-specific information is required, such as neonatal testing and intraoperative and ototoxicity monitoring.

In the prospective monitoring of ill subjects receiving ototoxic drugs, whether tested behaviorally or with objective measures, more rapid techniques which can provide sufficient information with which to make alternative treatment judgments will significantly increase the number of patients in whom ototoxicity can be detected before the occurrence of communicatively disabling hearing loss.
CONCLUSION

The overall goal of this research program is to monitor a broad spectrum of patients in order to develop techniques and methods for early detection and possible prevention of ototoxic hearing loss, regardless of the ability of the patient to provide behavioral responses. This goal will be pursued by designing and conducting studies using large patient populations which should yield refinement of the various behavioral and objective techniques presented here as preliminary findings. The key to success in this area is the early detection of ototoxic hearing loss, regardless of the response capabilities of the patient. Early detection enables steps to be taken for the prevention of handicapping hearing loss which would negate the necessity for rehabilitative measures.

ACKNOWLEDGMENTS

Portions of the data reported were obtained from information collected in an ongoing multi-site Rehabilitation Research and Development Service study at the following auditory research laboratories in cooperation with the participating investigators: VA Medical Center, Augusta, GA (Vernon Larson, PhD); VA Medical Center, Long Beach, CA (Richard Wilson, PhD); and VA Medical Center, West Los Angeles (Douglas Noffsinger, PhD).

In addition, the authors wish to acknowledge significant contributions to this research by Curtin R. Mitchell, PhD, Oregon Hearing Research Center; and David S. Phillips, PhD, Professor of Biostatistics at Oregon Health Sciences University.

REFERENCES

20. Piek J, Lumenta CB, Bock WJ. Brain-stem auditory