

Use of auditory brainstem responses for the early detection of ototoxicity from aminoglycosides or chemotherapeutic drugs

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Abstract—Effective objective HF (high-frequency) testing methodology provides for the early detection of ototoxic hearing loss because it typically progresses from high to low frequencies. Such early detection is considered necessary to prevent hearing loss from progressing into the frequency range important for understanding speech. Objective tests must be reliable, sensitive to hearing change, and time efficient. Auditory brainstem responses (ABRs) appear well suited to this task; however, current ABR techniques have limitations. Conventional clicks stimulate middle (1–4 kHz) rather than high frequencies (>8 kHz). Responses to HF tone bursts require considerable recording time. We hypothesized that using HF band-limited clicks (HF clicks) could overcome these limitations. Two different HF clicks, with bandwidths of 8–14 kHz were used to elicit ABRs. The current study compared responses among these stimuli. The results demonstrate the reliability of HF-click responses and of tone bursts presented in trains.

Key words: auditory brainstem responses, clicks, early detection, ototoxicity, tone bursts.

INTRODUCTION

The ultimate purpose of early detection and monitoring of ototoxic changes is to prevent, or to limit, hearing loss so as to preserve quality of life following treatment. Early detection of ototoxicity provides a physician with the necessary information to avoid the progression of hearing loss into frequencies critical for speech communication [1]. The high incidence of ototoxicity from aminoglycosides or chemotherapeutic drugs, and its potential

impact on a patients' subsequent quality of life, justifies the investment required to establish clinically effective monitoring methods [2,3]. Development of effective monitoring techniques ultimately should encourage more hospitals to establish monitoring programs. This, in turn, should improve patient care and reduce treatment costs associated with the effects of ototoxicity.

For those individuals who can provide appropriate responses, the behavioral measurement of high-frequency (HF) hearing sensitivity remains the most sensitive ototoxicity detection tool. A method to detect ototoxic changes targeting a narrow range of behavioral auditory thresholds near an individual's highest audible frequencies (>8 kHz) was developed in this laboratory [4]. HF behavioral audiometry works well in awake and alert subjects; however, approximately 30 to 40 percent of the patients at the Portland Department of Veterans Affairs (VA) Medical Center

Abbreviations: ABR = auditory brainstem response, CI = confidence interval, HF = high frequency, PC = personal computer, pe = peak equivalent, SD = standard deviation, SL = sensation level, SPL = sound pressure level, STB = single tone burst, VA = Department of Veterans Affairs.

This material was based on work supported by grant 0008 from the U.S. Department of Veterans Affairs, Medical Research Service and Rehabilitation Research and Development.

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who needed testing were hospitalized and too sick or otherwise unable to give reliable behavioral responses. Thus, another method for the early detection of ototoxicity is needed, preferably an effective objective test of HF auditory system function.

Techniques such as otoacoustic emissions, electrocochleography, and auditory brainstem responses have the potential for monitoring ototoxicity and have been used with various degrees of success [5–8]. These techniques can be used with unresponsive subjects, but the accuracy of the responses in relation to behavioral measures of auditory function is not known. Artifact-free otoacoustic emissions are difficult to obtain above 8 kHz, which severely limits its usefulness. Electrocochleography requires special electrode placement, which is more invasive, and its use has decreased in recent years. Auditory brainstem response (ABR) techniques using HF tone-burst stimuli (>8 kHz) have much to recommend its use [9,10].

There are several requirements for ototoxic early detection and monitoring to be applicable as a routine clinical test. The minimum requirements for such a test include responses that are (1) obtainable in a high percentage of patients, (2) reliable across test sessions, (3) sensitive to ototoxic change (that is, the highest frequencies that are audible to patients, usually >8 kHz), and (4) obtainable in a time-efficient manner.

Traditional ABR methods meet several of these requirements; however, improvements in sensitivity to HF threshold changes and in test time are needed to make ABR suitable as an objective indicator of early ototoxic hearing changes. ABRs can be obtained in patients who are awake and alert, sleeping, or even comatose. Subjects receiving ototoxic agents can show differences in ABR threshold, in Wave V latency, and waveform morphology compared to control subjects [9].

The most common stimulus for eliciting the ABR is a 100 μ s rectangular electrical signal, which produces a click. When this signal is transduced, by typical audiometric earphones, the spectral properties are broadband, usually with greatest acoustic energy between 1 and 4 kHz [9,11,12]. This click stimulus was used by Bernard et al. to evoke ABRs and to evaluate neonates who had been treated with aminoglycosides [8]. Similarly, Piek et al. used the click-evoked ABR to study comatose adult patients who had been treated with aminoglycosides [13]. Both groups of investigators reported an increase in the absolute latency of Wave V or a disappearance of Wave V. These early studies highlighted the potential of ABR for monitoring auditory changes in patients who are too young

to test behaviorally or are nonresponsive. Unfortunately, hearing loss can progress to the point that communication may become impaired before being detected with an ABR produced by these conventional clicks, because the responses are primarily from the 1 to 4 kHz region, which is most important for speech understanding.

This frequency region is too low to detect the first signs of ototoxicity, because the damage progresses from the higher frequencies to the lower frequencies for most ototoxic drugs [9,14,15]. For this reason, the emphasis shifted to an effort to obtain brainstem responses using HF (>8 kHz) tone bursts rather than conventional clicks. The frequency specificity of cochlear action potentials and ABRs elicited by tone bursts was determined by masking [16–18]. These studies demonstrated that just as HF pure-tone stimuli are used in behavioral evaluation, HF tone-burst stimuli could be used in evoked potential testing of auditory system function. These studies strongly suggested that it is possible to detect initial ototoxic changes in the high frequencies before the speech frequency range is affected. Gorga et al. obtained ABRs using HF tone bursts [11]. In serial tests, Fausti et al. demonstrated across-session test-retest reliability of these HF tone bursts, necessary for detecting ototoxicity [4].

At the time of these early studies, tone-burst stimuli for frequencies above 8 kHz were not available in commercial ABR systems and Dr. Fausti and colleagues at the Portland VA Medical Center designed and developed laboratory instrumentation to produce quality HF tone bursts. They showed that the ABRs elicited by HF tone bursts could detect ototoxicity earlier compared to ABRs from conventional click stimuli [9]. The time required to obtain ABR responses at several frequencies remained a limiting factor, especially for patients who could not tolerate lengthy test procedures [19,20].

The HF tone bursts elicit ABRs, which have very small amplitudes, often less than 0.2 μ V, presumably because only a small number of cochlear nerve fibers are involved in the response. Because the amplitude of these responses is very small, they are highly subject to degradation by background physiological noise. Thus, response acquisition usually requires considerably more averaging (e.g., 2,000 sweeps/average or more) than when conventional broadband clicks are used. The combination of additional averaging (with duplicate responses) and testing at several frequencies and intensities results in a lengthy test procedure. This is a serious difficulty, which prevents the routine clinical use of tone bursts for ABR.

A further difficulty in obtaining brainstem responses elicited by HF tone bursts for the detection and monitoring of ototoxicity is that when the highest audible frequencies of a patient are known, the tone bursts can be targeted to that frequency region and ABR testing can be reasonably time-efficient. However, if the highest audible frequencies are not known (often the case in hospitalized patients) and cannot be obtained using behavioral techniques, objective methods, such as ABR, must be used to identify the highest responsive frequency. To search for the highest responsive frequency using ABR is time-consuming, because online judgments regarding the presence or absence of responses must be made for each tone-burst frequency and level tested. An algorithm to reduce the search time was designed and tested; however, the testing time was still often greater than 90 min. With this extended testing, patients often became restless which increased the background physiological noise and degraded the brainstem response. After considerable effort, searching with single tone bursts (STBs) (at several frequencies and intensities) was determined not to meet the criterion of time-efficiency necessary for routine clinical testing (20 min or less of testing time). The need for a more rapid objective test became obvious.

Several techniques to reduce ABR testing time have been explored. Recent animal research has demonstrated that time savings can be obtained by delivering multiple stimuli of different frequencies and intensities in one "train" or sequence of stimuli [21–23]. A 20-stimulus train (four frequencies at five intensities) was used successfully in humans [24]. This multiple-stimulus technique significantly decreases testing time.

This current study compared the usefulness and reliability of HF-click stimuli that we have developed as well as tone-burst trains to determine their suitability for the early identification of ototoxicity. The HF-click stimuli sacrifice some frequency specificity to elicit larger, more robust responses in the HFs compared to HF tone bursts. To more rapidly obtain frequency-specific ABRs, we also investigated trains of HF tone bursts.

METHODS

Subjects

Method 1 was the HF-click comparison. For this method, 20 adult human subjects (15 females and 5 males), ranging in age from 21 to 43 years, mean age of

27, participated in this study. Method 2 was the comparison of STBs and tone-burst trains. Twenty adult human subjects (11 females and 9 males), ranging in age from 21 to 34 years, mean age 26, were tested in this study. Informed consent was obtained from all subjects in accordance with the standards of the VA institutional review board.

Acceptance criteria for subjects in both methods were (1) no history of ear disease, (2) normal immittance results, (3) hearing sensitivity <15 dB hearing level (HL) between 0.25 and 8 kHz, and (4) hearing sensitivity +1 standard deviation (SD) of laboratory norms between 8 and 14 kHz [25].

Equipment

All stimuli were digitally synthesized and controlled by a custom built, personal-computer (PC) based signal generation and data acquisition system (Advanced Logic Research, 90 MHz Pentium). A National Instruments DSP (digital signal processing) 2200 was used for precision signal generation. The digitally synthesized electrical signals were routed through Tucker-Davis Technologies precision modular instrumentation for attenuation and headphone buffering.

Calibration

We recorded the acoustic spectra of the tone bursts, the conventional click, and HF clicks with a 1/2-in. Brüel & Kjaer condenser microphone, mounted in a flat-plate coupler using a Hewlett Packard spectrum analyzer (model 35660A) [26]. We measured the peak-to-peak sound pressure level (SPL) using a Tektronix calibrated oscilloscope to determine the peak equivalent (pe) SPL.

Stimuli

The acoustic spectrum of the stimuli described shortly is the same as those shown in Fausti et al. [10]. The stimuli used in Method 1 were presented at 50 dB sensation level (SL) and at a rate of 22.3/s. The 50 dB SL was a compromise between a level that would yield responses a high percentage of the time and those that were uncomfortable to the subjects. The stimuli were as follows:

1. HF tone bursts, presented with alternating phase, at 8, 10, 12, and 14 kHz. The tone bursts had Cos^2 rise/fall times of 1 ms, 2 ms durations with no plateau. The STBs were delivered monaurally through a Koss Pro 4/X Plus headphone.

2. Conventional clicks produced by delivering a 100 μ s electrical square wave to a monaural TDH-50 ear-phone transducer. The acoustic spectrum of the standard or conventional click has considerable energy up to 4 kHz, with little energy in the 8 to 14 kHz region.
3. Flat HF clicks consisting of a flat acoustic spectrum across the frequency range 8 to 14 kHz. The acoustic spectrum of the flat HF click had less than +3 dB ripple from 8 to 14 kHz. Because of the audiometric threshold configuration of most subjects when the flat HF click is presented, the energy at 8 kHz would be expected to be at a greater SL than the higher frequencies (up to 14 kHz). This potentially biases the evoked response to 8 kHz. For this reason, a sloped HF click was also used.
4. Sloped HF clicks with the spectrum designed to more closely match the slope of the subject's audiometric threshold [25]. The acoustic spectrum of the sloped HF click had approximately +3 dB/kHz slope (18 dB total), between 8 and 14 kHz. Thus the sloped HF click had the potential to stimulate at more nearly equal SLs across the 8 to 14 kHz range.

We synthesized both the flat and sloped HF clicks by digitally adding seven tone bursts to produce the click waveforms with the desired level, rise time, duration, and bandwidth. The frequencies of the tone bursts were 8, 9, 10, 11, 12, 13, and 14 kHz. We adjusted the amplitude of each tone-burst component to achieve the desired flat or sloped HF-click spectra. A Cos^2 window shaped the rise time of both HF clicks. The resulting waveforms had 1 ms rise time with 2 ms durations and no plateau. Both HF clicks were delivered with alternating polarity (to minimize stimulus artifact), monaurally through Koss Pro 4/X Plus.

Method 2 used only tone-burst stimuli that had the same rise/fall times and duration as used in Method 1. The intensity levels (in decibels SPL) and time sequencing between stimuli were different. The decibels SPL was measured as described in the Calibration section, while the rate and sequences are described here. The STBs were delivered at the rate of 22.3/s as in Method 1. The two trains of sequenced tone bursts were constructed according to the principles described in Mitchell et al. [23]. One train, multiple intensity-single frequency, consisted of five intensities at one frequency, 5i1f. The time between stimuli in the train was 10 ms and the time between trains was 80 ms. The other train, a multiple intensity and frequency train, consisted of three intensi-

ties at each of five frequencies, 3i5f. Similarly, the time between stimuli in the train was 10 ms and the time between trains was 80 ms.

The ABR acquisition time using the single and multiple stimuli in the current study is of some interest. We presented single stimuli at 22.3/s with 2,048 repetitions to obtain each ABR average and thus required 92 s to obtain one average. The five-stimulus train (5i1f), which is 130 ms long, requires 266 s to obtain five averages, or 53 s per average. Using the 15-stimulus train (3i5f), which is 230 ms long, requires 471 s to obtain 15 averages, or 31.4 s per average.

PROCEDURES

ABR Electrode Placement

Subjects reclined comfortably in an acoustically and electrically shielded booth (Acoustic Systems, Model RE-245S). We recorded ABRs with gold cup electrodes, simultaneously from vertex-ipsilateral mastoid and vertex-contralateral mastoid using a common forehead ground. Single electrode impedance was maintained below 1,000 Ω , with interelectrode impedances no greater than 2,000 Ω . Vertex-ipsilateral recordings were scored for Wave V latency (peak) and amplitude (peak to trough). Vertex-contralateral recordings provided better IV-V separation and assisted in Wave V identification. Only the results from the ipsilateral recordings are presented herein.

ABR Recording

We amplified electrode outputs (200 or 500 kHz) and bandpass filtered from 100 to 3,000 Hz using Astromed-Grass (Model P511K) biological amplifiers/filters. A PC-based, 12-bit data acquisition board (EISA A2000, National Instruments Corp.) was used to digitize the bio-amplifier analog outputs. We digitally averaged responses to 2,048 stimulus presentations for each ABR waveform in a 10 ms analysis window using an acquisition-sampling rate of 50 k samples/s on each channel.

ABR Protocol

We determined behavioral threshold to each of the stimuli prior to data acquisition in each session. ABR data for each subject were collected in two sessions (S1 and S2). During each session, duplicate averages (R1 and R2) were obtained for each stimulus. Two audiologists,

Alison M. Bobal and Christopher L. Flick, scored each ABR average, and both scorers had to identify the presence of Wave V in an average for it to be considered a response.

In Method 1, the stimuli were (1) STBs at 8, 10, 12, and 14 kHz; (2) a conventional click; (3) the flat HF click; and (4) the sloped HF click. All single stimuli, tone bursts and clicks, were presented monaurally at 50 dB SL at a rate of 22.3/s. In Method 2, the stimuli were (1) STBs at 8, 10, 12, and 14 kHz; (2) tone-burst train at a single frequency at five intensities; (3) tone-burst train, three frequencies each at five intensities.

RESULTS

We examined two different ABR methods to determine the clinical use and reliability of brainstem responses for the early detection of impaired auditory sensitivity. Method 1 used HF clicks to obtain robust ABR Wave V amplitude responses from the HF region of the cochlea, and all stimuli were presented singly [10]. Responses elicited using HF clicks and traditional tone bursts were compared in each subject. Method 2 used single HF tone bursts as well as sequences or trains of these tone bursts. Trains were used to obtain responses more rapidly than tone bursts presented singly.

Our primary goal was to determine an objective method that could detect changes in hearing sensitivity from one test session to the next. The overall usefulness of such a method depends, in part, upon the ability to obtain a scoreable response a high percentage of the time when a stimulus is presented during baseline conditions (i.e., before administration of ototoxic drugs). We assessed this by determining the probability that a stimulus elicited a response on a given trial. For a stimulus to be clinically useful, it needs to have about a 90 percent probability that it will elicit a response on any given trial. A response must be reliable, since each subject serves as his or her own control in detecting changes in auditory sensitivity. This overall usefulness was determined by the amount of variability within each subject on a test-retest basis across sessions. For these reasons, a focus of this study was on this probability or percentage response as well as on the test-retest reliability in subjects whose auditory function was not likely to change during the study.

Usefulness or Percentage Response

In Method 1, we hypothesized that HF clicks would yield larger more robust responses than the tone bursts, because the HF clicks would stimulate neurons over a wider region of the cochlea (but still in the HF region) than a single-frequency tone burst. Two different HF clicks were used: one with relatively flat spectrum from 8 to 14 kHz and the other with sloping spectrum (+18 dB) over the same frequency range.

Table 1 is a summary of the percentage responses obtained from the various stimuli in the first method, each stimulus presented at 50 dB SL, four times to each subject (two runs in each of two sessions). The highest percentage responses were observed when the conventional click and the sloped HF click were used. The lowest percentages were observed when 12 and 14 kHz tone bursts were used. The percent response of most stimuli at 50 dB SL was about 90 percent or more, except for the tone bursts at 14 kHz. As previously reported, conventional and HF clicks produced larger amplitudes and more defined waveforms as compared to tone bursts [10]. We also found a trend of decreased response amplitude as a function of increasing frequency. The smaller amplitude at 14 kHz may account for the lower percentage response at this frequency.

The data from the second method are shown in **Table 2**. Overall, the percentage response is similar whether the stimuli were presented as STBs or in trains except at 14 kHz. The first frequency in the 3i5f train is 14 kHz, and it yielded a lowest percentage of responses at 100 dB SPL. The percentage response to 12 kHz (second frequency in the 3i5f train) was also unexpectedly low for all stimulus conditions.

Table 1.

Wave V responses (%) from different stimuli in Method 1. All stimuli were delivered at 50 dB SL, which is about 80 dB peak equivalent SPL.

Stimulus	% Response
Conventional Click	100
Flat HF Click	98
Sloped HF Click	100
8 kHz	92
10 kHz	98
12 kHz	86
14 kHz	75

SL = sensation level

SPL = sound pressure level

HF = high-frequency

Table 2.

Percentage response to single tone bursts (STBs) with 99% confidence intervals shown. Also percent response to 5-stimulus train (5i1f = 5 intensities at 1 frequency) and 15-stimulus train (3i5f = 3 intensities at 5 frequencies). Each stimulus was presented four times, the same as data in **Table 1**.

kHz	dB pe SPL	% Response		
		STB	5i1f	3i5f
8	50	—	27	—
	60	—	45	—
	70	58 ± 28	58	53
	80	75 ± 25	70	74
	90	83 ± 21	82	84
10	60	—	4	—
	70	—	63	—
	80	79 ± 23	50*	69
	90	67 ± 27	67	78
	100	67 ± 27	58	81
12	60	—	13	—
	70	—	30	—
	80	70 ± 26	59	38*
	90	71 ± 26	64	63
	100	69 ± 26	60	70
14	60	—	16	—
	70	—	21	—
	80	59 ± 28	76	32
	90	75 ± 25	72	47*
	100	91 ± 16	96	67*

*0.01 is probability of differences from STB.

pe = peak equivalent

SPL = sound pressure level

The data in **Table 2** show the percentage of auditory brainstem responses obtained from each of the stimuli used. To compare the percent response among the various stimuli, we considered the STB percent response a standard and calculated the 99 percent confidence interval (CI) (+) for each STB, as ± shown in **Table 2**. We then compared the percent response of stimuli in the trains (at an equal decibel SPL) with the CI to determine if it was significantly different from the STB percent response. Since 12 CIs were calculated and compared, we felt it appropriate to use the 0.01 rather than the 0.05 level for a

significant difference. On this basis, only four stimuli yielded percent responses that were statistically significantly different (using *t*-tests) from the STBs; two of these were at 14 kHz in the 3i5f train.

Across-Session Reliability

We determined the ABR Wave V test-retest variability, across sessions, for each method. The across-session differences between responses obtained (on different days) were calculated for each subject. The across-session latency and amplitude differences obtained with the first method are shown in **Table 3**.

A repeated measures analysis of variance (ANOVA) of the mean differences showed no significant difference between the stimuli ($p > 0.01$). Although the conventional click had a smaller SD (for latency) than the other stimuli, an *F*-test found no significant difference between the SDs ($p > 0.01$).

In **Table 4**, the Wave V latencies and amplitudes elicited by the stimuli used in Method 2 are shown. They are the STBs and the tone bursts in the 5- and 15-stimulus trains. The small amplitudes elicited by these tone bursts, whether presented singly or in a train, are notable, as previously discussed. The latencies elicited by the STBs are consistently shorter than when the same tone bursts are presented in a train. This finding indicates that the responses from stimuli in these trains exhibit some adaptation, fatigue, or other process. This process probably does not pose a significant problem for the early detection and monitoring of ototoxicity because individuals serve as their own control.

The across-session differences in Wave V for stimuli presented singly and in the two trains are shown in **Table 5**.

Table 3.

Across-session Wave V latency and amplitude differences, means, and standard deviations (SDs) for each stimulus used in first method.

Stimulus	Latency (ms)		Amplitude (μV)	
	Mean (S2-S1)	SD	Mean (S2-S1)	SD
Conventional Click	0.03	0.14	0.01	0.05
Flat HF Click	-0.03	0.18	-0.01	0.03
Sloped HF Click	-0.07	0.23	0.00	0.04
8 kHz	-0.02	0.22	0.00	0.05
10 kHz	-0.05	0.22	-0.01	0.04
12 kHz	-0.03	0.24	0.00	0.03
14 kHz	0.01	0.25	0.01	0.03

Table 4.

Average ABR latencies and amplitudes of Wave V for subjects tested in Method 2.

kHz	dB SPL	Latency (ms)			Amplitude (μ V)		
		STB	5i1f	3i5f	STB	5i1f	3i5f
6	70	—	—	7.33	—	—	0.12
	80	—	—	6.99	—	—	0.18
	90	—	—	6.66	—	—	0.21
8	50	—	7.43	—	—	0.11	—
	60	—	7.26	—	—	0.13	—
	70	6.98	7.10	7.05	0.17	0.14	0.14
	80	6.72	6.81	6.90	0.18	0.16	0.18
	90	6.43	6.59	6.66	0.21	0.19	0.20
10	60	—	7.36	—	—	0.09	—
	70	—	7.46	—	—	0.11	—
	80	7.28	7.43	6.98	0.11	0.11	0.15
	90	6.87	7.08	6.85	0.13	0.12	0.17
	100	6.78	6.84	6.66	0.14	0.14	0.19
12	60	—	7.30	—	—	0.13	—
	70	—	7.20	—	—	0.11	—
	80	7.06	7.01	7.22	0.14	0.11	0.12
	90	6.85	7.01	7.12	0.13	0.14	0.14
	100	6.72	6.92	7.05	0.14	0.14	0.15
14	60	—	7.46	—	—	0.09	—
	70	—	7.48	—	—	0.10	—
	80	7.09	7.23	7.19	0.12	0.11	0.12
	90	6.90	7.11	7.06	0.14	0.13	0.13
	100	6.78	7.01	7.06	0.13	0.16	0.13

ABR = auditory brainstem response

SPL = sound pressure level

STB = single tone bursts

5i1f = train, five intensities at one frequency

3i5f = train, three intensities at five frequencies

This reliability did not vary appreciably with frequency or intensity, and no differences were apparent between tone bursts presented singly or in a train. Neither the differences nor the SDs of the differences showed a statistically significant trend with intensity. (One might expect that at the higher intensities, the response would be larger and have less variability.) This stability in the intersession difference may have been due in part to the rather stringent criterion for scored responses (i.e., both scorers had to identify a response in an average for it to be accepted).

Table 5.

Across-sessions test-retest differences for three stimulus conditions used in Method 2.

Freq Hz	dB pe SPL	Latency (ms)			Amplitude (μ V)		
		STB	5i1f	3i5f	STB	5i1f	3i5f
6	70	—	—	0.15	—	—	-0.01
	80	—	—	0.08	—	—	0.01
	90	—	—	-0.01	—	—	0.01
8	50	—	-0.08	—	—	-0.05	—
	60	—	-0.09	—	—	-0.01	—
	70	0.01	-0.07	0.06	0.01	0.02	-0.01
	80	0.02	0.01	0.10	0.00	0.00	-0.02
	90	-0.03	0.03	0.03	0.00	-0.02	-0.04
10	70	—	-0.07	—	—	0.01	—
	80	0.05	-0.03	0.04	0.02	—	0.01
	90	-0.11	-0.09	0.06	0.07	0.10	-0.02
	100	0.06	0.04	0.09	-0.01	0.01	0.01
12	70	—	0.26	—	—	0.00	—
	80	-0.05	0.08	0.03	-0.08	0.11	-0.02
	90	-0.13	-0.14	0.16	-0.01	-0.05	0.01
	100	-0.16	-0.06	0.01	0.04	-0.03	0.01
14	80	0.05	0.08	-0.03	-0.04	0.02	-0.02
	90	0.02	0.15	0.12	-0.02	-0.01	0.00
	100	-0.11	0.07	0.04	-0.03	-0.02	0.01

pe = peak equivalent

SPL = sound pressure level

STB = single tone bursts

5i1f = train, five intensities at one frequency

3i5f = train, three intensities at five frequencies

DISCUSSION

The usefulness of an ABR method depends, in part, upon the probability of a response being elicited by the stimuli employed. This metric is not commonly reported in ABR studies. The percentage of missing responses can only be inferred in some studies [27,28]. It is generally considered that stimuli above behavioral threshold will consistently yield an ABR. The lack of responses is usually considered to be due to the presence of physiological noise or other noise. Responses with an insufficient number of sweeps are ignored. However, in the detection and monitoring of auditory sensitivity or similar applications, missing responses are of considerable importance. Early

studies of middle latency responses reported the percent response at different stimulus intensities [29,30]. Their data of percent response with intensity are similar to that found in the present study. In the former case, levels of 60 dB SL were necessary to reach 85 percent response, and in the latter, 45 dB reached 94 percent. These studies, as well as the present study, suggest that levels of about 50 dB SL are required to achieve a 90 percent response probability, under typical recording conditions. Both methods in the current study found a lower percent response at the highest frequencies 12 and 14 kHz.

The reliability of electrocochleographic and brainstem responses has been reported in several studies [4,31–34]. The intersession or across-session variability within each subject is pertinent to the detection of changes in sensitivity. Fausti et al. reported the intra-subject, intersession reliability of ABRs to single HF tone bursts (>8 kHz) and later similar reliability of sequenced or trains of tone bursts [4,32]. The current study found no significant differences between response reliability to clicks presented singly or HF tone bursts presented singly or in trains. Also the reliability did not vary significantly with stimulus frequency or intensity (**Tables 3 and 4**).

The across-session reliability has been reported for electrocochleography (Wave I of the ABR) by Mori et al. [31], Roland et al. [33], and Park and Ferraro [34]. In each case, the reliability was considered sufficient to detect significant changes in auditory function and suggests its usefulness in ototoxicity studies.

The sequence or train of stimuli method was successful in reducing the test time by almost 90 percent in animals [23]; however, less timesavings (80%) were achieved in humans, in part, because shorter trains of stimuli were used (15 vs. 56 stimuli). Further, the percent response was reduced probably because of the small amplitude of the HF tone bursts used to elicit the brainstem response [10].

In the current study, four different stimulus types were investigated and questions arose as to what might be the best method. Because a sizable timesavings exists when stimuli are presented in trains, using stimulus trains would be advantageous. A method that appears promising is to use two trains. The first would contain multiple frequencies and intensities and could locate the highest frequency at which an ABR is obtained in a particular individual. The second train would contain the highest frequency at three to five intensity levels. The second train would be used for serial testing. This approach would locate, confirm, and

then monitor responses at this highest frequency. Other variations on this approach could also be used.

CONCLUSIONS

This study compared the reliability and usefulness of different ABR stimuli for the early identification of ototoxicity. In Method 1, ABRs elicited by single tone-burst stimuli were compared with those elicited by conventional and HF clicks. The impetus for this study was that while tone bursts have been shown effective in eliciting reliable ABRs, the response amplitude is small and the testing time is lengthy. HF clicks produced a larger more robust response and were more time-efficient than STBs. In Method 2, single as well as trains of tone bursts elicited ABRs. The trains of stimuli allow the more efficient data collection.

All stimuli tested produced reliable responses both within and across sessions. Conventional and HF clicks elicited more robust responses than tone bursts. These click responses are easily identifiable and highly reproducible within individuals. Conventional clicks, however, do not stimulate HF regions of the cochlea and are not suitable for detecting ototoxicity. HF-click ABRs are suited to the early detection of ototoxicity because the click spectra are limited to the HF region (8 to 14 kHz). HF clicks also offer the advantage of time-efficiency as compared with STBs. Trains of tone bursts yielded responses very similar to STBs with the advantage of considerable timesavings. HF clicks had a higher response probability, which gives them somewhat more usefulness than tone bursts for ototoxic detection and monitoring.

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Submitted for publication May 28, 2003. Accepted in revised form October 21, 2003.