Detection of Ototoxicity

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ABSTRACT

Ototoxicity monitoring is particularly critical in patients receiving platinum-based chemotherapy or long-term aminoglycoside antibiotic administration. Furthermore, as new otoprotective agents are developed, audiologists need to not only be able to monitor for ototoxicity but know the various criteria for early detection of ototoxicity and how to grade ototoxic adverse events. The three primary methods for ototoxicity monitoring are conventional audiometry, high-frequency audiometry, and otoacoustic emissions. However, early detection and adverse event criteria depend primarily on conventional and high-frequency audiometry. No consensus exists on determining significant changes in otoacoustic emissions secondary to ototoxic drugs. Also, no consensus exists on how to monitor for tinnitus, although it is a common complication in these patients. Currently, tinnitus surveys can be helpful. A baseline evaluation is critical for accurate interpretation of auditory threshold results. Thus, a team approach is needed to ensure adequate care of these children. For clinical trials and in reading the literature, audiologists need to be aware of the American Speech Language Hearing Association's 1994 criteria for detection of ototoxic change, and the Common Terminology Criteria for Adverse Events, Brock, and the Change scales for classification of adverse events. These methods and scales are reviewed and discussed.

KEYWORDS: Ototoxicity, pediatric, high-frequency audiometry, ototoxicity monitoring, early detection, adverse event, grading scales

Learning Outcomes: As a result of this activity, the participant will be able to (1) list the optimal methods for monitoring children for possible ototoxic hearing changes, and (2) compare and contrast the various methods for determining significant ototoxic change and grading ototoxic adverse events.

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DETECTION OF OTOTOXICITY

Several options exist for monitoring ototoxic changes. The measures selected are generally based on the known or suspected ototoxic profile of the drug. Many ototoxicity monitoring protocols are based on the ototoxic profile of platinum-based chemotherapeutics and aminoglycoside antibiotics because they are widely used and have a relatively high incidence of ototoxicity. Because ototoxicity of platinum-based chemotherapeutics and aminoglycoside antibiotics almost always starts with hearing threshold shifts at the highest audiometric frequencies, clinical ototoxicity monitoring programs for those agents focus on early detection of high-frequency changes[1,2]. However, other ototoxins, such as difluoromethylornithine (DFMO), loop diuretics, and salicylates, may cause a wide variety of other audiometric configurations.[3–5] For a drug with an unknown or poorly defined ototoxic profile, it would seem logical to first focus on whether or not the drug causes hearing loss in the conventional-frequency range and if so, whether it causes auditory changes reaching adverse event criteria.

There are three primary approaches to monitoring drugs for ototoxicity: the basic audiological assessment, high-frequency audiometry, and otoacoustic emissions (OAEs).[2,6,7] Other techniques such as auditory brain stem response may be used for a given patient but are not standard monitoring techniques,[1] although they may be used to detect changes in the central auditory system.[8] The basic audiological assessment focuses on pure-tone air conduction thresholds in the conventional-frequency range of 0.25 to 8 kHz. Bone conduction thresholds are used as needed to determine if an air–bone gap or conductive component exists as a part of any hearing loss observed. Immittance audiometry is sometimes included to assess the status of the tympanic membrane and middle ear. For most ototoxins, the primary ototoxicity of concern is cochleotoxicity, which would be expressed as a sensorineural hearing loss. However, in the case of an agent that causes otitis externa, occlusion of the ear canal secondary to swelling or dermatitis of the ear canal, or changes in the tympanic membrane, auditory changes could occur in the absence of cochleotoxicity. Conductive threshold changes would probably not start or be worse for frequencies above 8 kHz.

No consensus exists regarding methodologies to monitor for drug-induced tinnitus, although several options exist. One option is the Tinnitus Ototoxicity Monitoring Interview (TOMI), which is specifically designed for that purpose[1] but has not yet been validated in large-scale clinical trials involving ototoxicity. Another option is the Tinnitus Severity Index (TSI) questionnaire, which has been documented in several ways. The TSI was derived from detailed evaluation of over 2000 patients.[9,10] It is a 12-item scale that quantifies the magnitude of tinnitus-related impairment, disability, and handicap according to guidelines established by the World Health Organization.[11,12] Both the TOMI and the TSI were developed at the Portland, Oregon, Veteran's Administration and the Tinnitus Clinic of the Oregon Hearing Research Center. The Tinnitus Handicap Inventory (THI) is the most widely used and validated tinnitus questionnaire.[13,14] The THI has high internal consistency and reliability (Cronbach's $\alpha = 0.93$) and test–retest stability ($r = 0.92$).[14] However, no articles exist in the literature reflecting its use for clinical trials of a known or suspected ototoxin. All of these scales use subjective ratings for tinnitus. But, subjective ratings for tinnitus, using a scale from 0 to 10, are well documented by several investigators.[9,13,15,16] Such ratings are quickly and easily administered, and can be efficient measures for quantifying tinnitus treatment effects. The subjective loudness rating for tinnitus captures the aversive aspect of tinnitus, in a similar manner to that of pain rating scales, which are widely used by pain experts to quantify the aversive aspect of chronic pain. It has the advantage that it does not require the subject to try to recall his or her tinnitus problems during a preceding time interval (such as a week or more), but instead can be given as an immediate and current rating of the tinnitus magnitude.

The Basic Battery

The basic battery is probably the most important methodology for determining if a drug is ototoxic in humans.[2,6,7,17] Otoscopy is routinely

conducted prior to any audiological assessment. At baseline, the basic battery includes pure-tone air conduction thresholds for octave bands from 0.25 to 8 kHz generally measured using a modified Hughson-Westlake approach.[18] If air-conduction thresholds are 15 dB hearing level (HL) or greater at any test frequency, bone conduction testing is then conducted to determine if any significant (greater than 10 dB) air–bone gaps exist that would indicate a conductive component. Sometimes immittance audiometry is included at baseline and in other cases it is only included if a significant air–bone gap is detected. Immittance audiometry is advisable at baseline to prevent any fluctuant conductive component from confounding data interpretation later in the study. Clinically, word recognition testing using 50-word lists is frequently included at baseline if the patient will be receiving a known ototoxin, because understanding the change in word recognition from baseline can assist in patient management, including counseling and fitting amplification if needed. However, word recognition is not generally included as a criterion for determining if ototoxicity has occurred.[1,2,6,7,17] Detection and quantification of ototoxicity is based on pure-tone thresholds obtained via serial audiograms.[1,2,6,7,17]

High-Frequency Audiometry

High-frequency audiometry, pure-tone air conduction threshold testing for frequencies above 8 kHz, is used for early detection of ototoxicity for ototoxins that preferentially affect the basal region of cochlear outer hair cells, such as platinum-based chemotherapeutics and aminoglycoside antibiotics.[1,2,7] High-frequency audiometry has no proven efficacy for early detection of ototoxicity in drugs that do not preferentially affect the basal region of the cochlear outer hair cells such as DFMO, salicylates, and loop diuretics. Because many adult patients, particularly middle-aged or geriatric patients, may not have measurable hearing above 8 kHz, even when high-frequency audiometry monitoring is desirable, it may not be practicable in every patient.[19–25]

Procedures for ototoxicity monitoring using high-frequency audiometry are now well established,[2,7,17] although some abbreviated methods have been suggested.[1] Although intersubject variability in high-frequency thresholds is high, even among subjects with normal thresholds in the conventional-frequency range,[26] for a given individual with a baseline hearing test, intrasubject variability is low using current equipment and calibration procedures.[7,17,27–32]

One limitation for high-frequency audiometry in multicenter clinical trials is that high-frequency audiometry equipment is not available in the majority of audiology clinics because it is generally only used in major medical centers for specific patient populations. Thus, most audiology clinics do not invest in the extra equipment and calibration procedures required.

Otoacoustic Emissions

OAEs are acoustic signals generated by the cochlear outer hair cells. The most commonly recorded types of OAEs include spontaneous OAEs, which occur in the absence of an eliciting stimulus; transient OAEs, which occur in response to repeated but single transient stimuli (e.g., clicks); and distortion product OAEs, which occur in response to two stimuli of different frequencies being introduced to the ear canal.

OAEs can be a useful part of a clinical ototoxicity monitoring program because they are generally quick, do not require a behavioral response from the patient, and specifically reflect cochlear outer hair cell status.[2,7] For an ototoxin that targets the basal region of cochlear outer hair cells (e.g., aminoglycosides, platinum-based chemotherapeutics), OAEs can provide an early warning of ototoxic change prior to pure-tone threshold changes in the conventional-frequency range.[31,33–39] In general, distortion product OAEs tend to provide an earlier warning than transient OAEs.[39] However, in comparative studies in children receiving platinum-based chemotherapeutics, high-frequency audiometry generally detected ototoxic change earlier than distortion product OAEs.[40,41]

OAEs also have several disadvantages for ototoxicity monitoring. Because they are low-amplitude acoustic signals emanating from the

cochlea, they generally require a normal outer and middle ear for the OAE to be transmitted to the recording microphone. Thus in patients with otitis media, as may occur in immunosuppressed or pediatric patients, OAEs may not be reliably present in serial recordings. In patients with otitis externa, the requirement of a hermetic seal for the ear canal probe may prove to be too painful or unobtainable. Further, cerumen occlusion precludes OAE recording. However, the biggest disadvantage of OAEs in ototoxicity monitoring is that, unlike conventional and high-frequency audiometry, there are no widely accepted and validated criteria to determine significant ototoxicity change. Thus methodology and interpretation of OAE findings for ototoxicity vary widely.

Serial Monitoring after the Baseline Assessment

Serial monitoring for ototoxicity depends on several factors including patient considerations (e.g., age, Karnofsky score, availability for testing, hearing status at baseline) and the ototoxic profile of the agent the patient is taking. In general, pure-tone air conduction thresholds in the conventional-frequency range will be monitored and if the ototoxin is known to target cochlear outer hair cells in the basal turn, high-frequency audiometry will be included. If a significant change in pure-tone thresholds from baseline is noted, further diagnostic testing is performed to determine if the change is conductive or cochleotoxic. Immittance audiometry is used to assess tympanic membrane and middle ear status. Bone conduction threshold testing for frequencies between 0.25 and 4 kHz can be used to determine if the threshold shift is conductive or sensorineural. However, bone conduction testing cannot be performed for frequencies above 4 kHz. If a baseline hearing test was not performed, the degree of threshold shift, if any, cannot be interpreted.

If OAEs were conducted at baseline, they may be repeated on serial testing and can provide individual ear information on cochlear outer hair cell function. However, cerumen occlusion, otitis externa, or otitis media can preclude OAE recording. Furthermore, as previously discussed, there is no consensus on criteria for significant ototoxic change as measured by OAEs.

The frequency and timing of ototoxicity monitoring depends on the known or suspected ototoxic profile of the drug being administered to the patient.

Determination of Significant Ototoxic Change

Several significant ototoxic change criteria have been proposed over the years. The most widely used criteria for early detection of ototoxic change are described in the guidelines of the American Speech Language Hearing Associations (ASHA) Criteria for Early Detection of Ototoxic Change 1994 and the American Academy of Audiology Position Statement and Clinical Practice Guidelines 2009. The purpose of these criteria is to detect ototoxic change before significant change in the patient's communication abilities occurs. To be considered a significant ototoxic change, pure-tone air conduction threshold shift must meet one of the following three criteria: (1) $\geq$ 20-dB decrease at any one test frequency, (2) $\geq$ 10-dB decrease at any two adjacent frequencies, or (3) loss of response at three consecutive frequencies where responses were previously obtained. Changes are always computed relative to baseline measures and must be confirmed by repeat testing, generally within 24 hours. These criteria minimize random variability by using adjacent test frequencies. These criteria are sensitive to ototoxic change and have not been shown to yield false-positive findings for air-conduction threshold testing in either the conventional- or high-frequency ranges.[17,32,42] However, the ASHA 1994 criteria are only designed for early detection of ototoxic change and are not designed to indicate degree of ototoxic change or classify the degree of an adverse event, such as in clinical trials.

To classify the degree of ototoxic threshold shift or the grade of ototoxic adverse event, scales of hearing loss are used. There are several scales for recording and grading ototoxic adverse events. The purpose of these scoring systems is to categorize the degree of change and to compare across clinical trials or treatments in groups

of patients. All of these scales are based primarily on pure-tone air conduction thresholds in the conventional-frequency range.

The most commonly used system to grade adverse events in U.S. clinical trials is the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades. The recent version of these criteria as revised in October 2009 is as follows.

CTCAE 4.0

Ear and Labyrinth Disorders: Hearing Impaired

GRADE 1

- Adults enrolled on a monitoring program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of 15 to 25 dB averaged at two contiguous test frequencies in at least one ear or subjective change in the absence of a grade 1 threshold shift.
- Pediatric (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift >20 dB at 8 kHz in at least one ear and does not meet criteria for grade 2 or greater.

GRADE 2

- Adults enrolled in monitoring program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of >25 dB averaged at two contiguous test frequencies in at least one ear.
- Adults not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental assistive listening device.
- Pediatric (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift >20 dB at 4 kHz and above in at least one ear and does not meet criteria for grade 3 or greater.

GRADE 3

- Adults enrolled in monitoring program (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): threshold shift of >25 dB averaged at three contiguous test frequencies in at least one ear; therapeutic intervention indicated.
- Adults not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated; limiting self-care assistive listening device.
- Pediatric (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; Threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language-related services indicated.

GRADE 4

- Adults: profound bilateral hearing loss (threshold >80 dB HL at 2 kHz and above); nonserviceable hearing.
- Pediatric: audiological indication for cochlear implant and additional speech-language-related services indicated.

Another system originally developed in England to grade the degree of ototoxic hearing loss in pediatric patients receiving platinum-based chemotherapeutics is the Brock Scale. For patients with no baseline audiometric testing, threshold is assumed to be less than or equal to 5 dB at all frequencies. That assumption is made because in children permanent sensorineural hearing loss is less common than in adults. However, a baseline hearing assessment is still advisable.

Brock's Hearing Loss Grades

Grade 0: hearing thresholds less than 40 dB at all frequencies.
Grade 1: thresholds 40 dB or greater at 8000 Hz.
Grade 2: thresholds 40 dB or greater at 4000 to 8000 Hz.
Grade 3: thresholds 40 dB or greater at 2000 to 8000 Hz.
Grade 4: thresholds at 40 dB or greater at 1000 to 8000 Hz.

Recently, Chang et al 2010[43] developed the Chang scale (Table 1). This scale not only categorizes the degree of ototoxic change but

Table 1 Sensorineural Hearing Threshold (dB HL)

Chang Grade	Bone Conduction on Air Conduction with Normal Tympanogram
0	≤ 20 dB at 1, 2, and 4 kHz
1a	≥ 40 dB at any frequency 6 to 12 kHz
1b	> 20 and < 40 dB at 4 kHz
2a	≥ 40 dB at 4 kHz and above
2b	> 20 and < 40 dB at any frequency below 4 kHz
3	≥ 40 dB at 2 or 3 kHz and above
4	≥ 40 dB at 1 kHz and above

dB HL, decibel hearing level.

addresses information frequently used in patient management. As does the Brock scale, the Chang scale assumes normal hearing prior to chemotherapy if no baseline data are available. The Chang scale also is designed to detect ototoxic threshold change secondary to platinum-based chemotherapeutics as is the Brock scale. Because the Chang scale was so recently developed, it is not yet in widespread clinical use.

CONCLUSION

In summary, a variety of methods exist for monitoring ototoxicity. Some are designed for early detection of ototoxicity, some for grading ototoxicity, and some for obtaining additional information about ototoxic change and its site of lesion. Because not all ototoxins, or suspected ototoxins, affect the auditory system in the same way, methodologies must be designed for the drug and patient population in question.

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