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Audiological Monitoring of Patients Receiving Ototoxic Drugs

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Over 200 medications commonly prescribed for the treatment of cancers and some infections can cause inner ear damage, or ototoxicity (ASHA, 2004). Ototoxicity can result in auditory and / or vestibular dysfunction, and the effects can be temporary, but are often permanent. Symptoms of ototoxicity include tinnitus, dizziness, and difficulty understanding speech in noise. Approximately 4 million patients annually in the United States are at risk for hearing loss from aminoglycoside antibiotics (e.g. gentamicin) and platinum-based chemotherapy agents (e.g., cisplatin). Loop diuretics (e.g., furosemside) can also cause ototoxicity, particularly when administered concurrently with other ototoxic drugs (Brummett, 1980). Furthermore, noise exposure has a synergistic effect, increasing the risk of hearing loss during therapeutic treatment with ototoxic drugs (Brown, Brummett, Fox, & Bendrick, 1980).

For patients treated with ototoxic drugs, hearing loss can adversely affect speech communication, coping skills, and quality of life. Ototoxicity is poorly correlated with drug dosage (Blakley & Meyers, 1993), peak serum levels (Black & Pesznecker, 1993), and other toxicities, such as renal toxicity (Rougier et al., 2003), making it difficult to predict when symptoms will present. Ototoxic hearing loss often progresses unnoticed until a communication problem becomes apparent, signifying that hearing loss within the speech frequency range has occurred. Therefore, the early detection of ototoxicity must involve direct auditory function assessment.

Purpose and Benefits of Monitoring

Serial ototoxic monitoring tests utilize a hearing change criterion value defined as the difference value between two measurements of the same test recorded on separate occasions. Monitoring tests must be sensitive to ototoxic damage (high hit rate), specific (low false positive rate), and reliable (low test-retest variability) across measurements. Significant clinical

change occurs when the difference value between successive measurements exceeds documented normal variability.

Prospective audiometric testing and the early identification of ototoxic hearing loss are critical to facilitate alternative treatments, wherever possible, that can minimize or prevent communication impairment. If hearing changes are identified, physicians may alter dosages or discontinue treatment with current medications, switch to less toxic medications, or continue treatment and prepare the patient and family to cope with hearing loss. If no hearing changes are noted, physicians may aggressively treat the disease with increased confidence. Early identification and monitoring of ototoxic hearing loss provides opportunities for counseling regarding communication strategies, the synergistic effects of noise exposure with ototoxic medication, and implementation of aural rehabilitation.

Early Identification

Because ototoxic damage begins in the cochlear base and progresses toward the apex (Barron & Daigneault, 1987), use of clinical tests sensitive to changes in the basal (high frequency) region provide the earliest detection of ototoxic damage. Ototoxicity identification before speech frequencies are compromised can alert providers prior to impairment of communication ability. The foundation of ototoxicity monitoring is the serial collection of pure-tone behavioral thresholds. Ultra-high frequency audiometry and evoked otoacoustic emission (OAE) testing are measurement techniques that identify ototoxic damage earlier than conventional pure-tone threshold testing.

Serial hearing assessment at the highest audible frequencies for each patient using ultra-high frequency thresholds (> 8 kHz) allows early detection of ototoxicity before speech frequencies are affected (Fausti et al., 1993). The majority (94%) of test-retest differences reported for ultra-high-frequency thresholds using modern equipment were within $\pm$ 10 dB for frequencies between 9 and 14 kHz in patients not receiving ototoxic drugs, thus showing good reliability. False positive rates, which indicate threshold changes in subjects not exposed to ototoxic drugs, were low (0-7%) both in a sound booth and on the hospital ward under controlled conditions (see Gordon, Phillips, Helt, Konrad-Martin, & Fausti, 2005, for a detailed review of this literature). Therefore, the use of ultra-high frequency audiometry is a highly reliable, sensitive, and specific technique for detecting ototoxicity.

Full-frequency pure-tone threshold testing is impractical for those who fatigue easily and are incapable of completing lengthy behavioral tests. Fausti and colleagues have proposed a shortened procedure targeting a limited range of frequencies near the upper frequency limit of hearing for each individual (Fausti et al., 1999). The highest frequency with a threshold at or below 100 dB SPL followed by the next six lower adjacent frequencies in 1/6-octave steps, defines a one-octave range of frequencies found to be a sensitive range of ototoxicity (SRO). In rare cases, ototoxic damage may occur first at a lower frequency; however, the reported hit rate for this shortened SRO test protocol is approximately 90% in large groups of adult patients with ototoxic hearing changes (Fausti et al., 2003). Ultra-high frequency audiometry has been successfully evaluated in children above age 5, although effectiveness of the SRO protocol has not yet been studied in children receiving ototoxic drugs. The SRO protocol improves clinical efficiency for serial monitoring while maintaining high sensitivity to ototoxic damage. Standardized criteria have been developed for use with pure-tone thresholds obtained at conventional and ultra-high frequencies, and these criteria have proven effective in large groups of subjects receiving ototoxic drugs.

Another measure of early ototoxicity is the OAE, an objective (non-behavioral) measure that can be used in patients who cannot respond reliably to behavioral testing techniques. Initial ototoxic damage is typically confined to the outer hair cells in animals treated with ototoxic drugs (Hodges & Lonsbury-Martin, 1998). Evoked OAEs are acoustic responses generated by outer hair cells within the cochlear end organ, suggesting that OAEs may be a sensitive indicator of ototoxic damage. Distortion product OAEs (DPOAEs), responses elicited using two tones, are particularly effective for the early detection of ototoxicity. Researchers have shown that changes in OAEs preceded changes in behavioral (pure-tone) thresholds in patients receiving ototoxic drugs (Lonsbury-Martin & Martin, 2001; Stavroulaki, Apos-tolopoulos, Segas, Tsakanikos, & Adamopoulos, 2001). Researchers have produced normative data demonstrating excellent test-retest reliability of DPOAEs (e.g., Franklin, McCoy, Martin, & Lonsbury-Martin, 1992). These results suggest that OAEs can be used to monitor ototoxic damage with a high degree of reliability and sensitivity. Furthermore, OAEs can be obtained in infants, young children, and sedated adults.

High frequency (8-14 kHz) auditory brainstem responses (ABR) using narrow band filtered clicks can also provide early detection of ototoxic change for patients with limited responsiveness (Fausti et al., 1992). ABRs are often used to estimate thresholds and usually are within 15 dB of behavioral thresholds. These results can be useful to determine threshold changes

over time. It is important to remember that ABRs and OAEs are not tests of hearing, but rather test the responsiveness and stability of the auditory system during drug treatment. In this way, these objective measures are an effective measure of ototoxic-induced changes in auditory function.

Detecting Hearing Change

To detect ototoxicity, it is necessary to monitor a response that is both sensitive to ototoxic damage and reliable over time. Serial audiograms using conventional and ultra-high frequency threshold testing, evoked OAEs, and ABR can effectively detect clinically significant changes in auditory function. ASHA (1994) developed hearing change criteria for serial audiograms (which must be confirmed by retest) which include: $\geq$20 dB pure-tone threshold shift at one frequency, $\geq$10 dB shift at two consecutive test frequencies, or threshold response shifting to "no response" at three consecutive test frequencies. The use of a large (20 dB) single frequency threshold shift or comparatively smaller shifts at adjacent frequencies was established by evidence suggesting that threshold shifts at adjacent test frequencies indicate more systematic change compared to shifts at any single frequency and are less likely to result in false positive responses (Simpson, Schwan, & Rintelmann, 1992).

Currently, there are no accepted protocols or criteria for ototoxic change using objective measures. However, test-retest variability in control subjects can provide the basis for developing ototoxic monitoring protocols. Roede, Harris, Probst, and Xu (1993) advocated change criteria based on the mean test-retest variability of the OAE plus 2 standard deviations, which was 5.4 dB at 70 dB SPL and 8.3 dB at 55 dB SPL in the population tested. Thus, an OAE change was considered significant if it were greater than the normal variability observed in approximately 95% of subjects not receiving ototoxic drugs. Beattie, Kenworthy, and Luna (2003) proposed similar change criteria using standard error of the measurement difference to determine significant OAE test-retest differences, suggesting that for OAEs obtained at 65 dB SPL, the amplitude difference must exceed 7 dB between 1-4 kHz to indicate a true change. Differences in OAE change criteria reported in the literature are likely related to differences in the equipment, OAE parameters, and statistical methods. Verifying that each clinic's OAE test-retest variability is comparable to the literature is essential, as variability is increased by inconsistent probe placement and in patients versus healthy subjects. Further research is needed to validate the use of these OAE change criteria in large groups of subjects receiving ototoxic drugs.

Ototoxic change criteria for ABRs have also been based on test-retest reliability examined in subjects not receiving ototoxic drugs. Changes in ABRs elicited by high frequency tonebursts have been defined as a 0.3 ms latency shift for wave I or wave V or the change of a previously scoreable response to unscoreable (Fausti et al., 1992). In a study of neonates receiving gentamicin, ABR change criteria defined as ABR latency delay > mean test-retest variability in non-drug exposed neonates plus 2 standard deviations, was 1.8 $\pm$ 0.8ms for wave I and 5.7 $\pm$ 0.8ms for wave V (De Lauretis, De Capua, Barbieri, Bellussi, & Passali, 1999). Again, further research is needed to validate the use of ABR change criteria in studies involving subjects receiving ototoxic drugs.

Implementing a Program

Identifying and Scheduling Patients

Implementing an ototoxicity early detection and monitoring program requires the identification of patients at highest risk for ototoxicity, including those receiving highly ototoxic medications (cisplatinum, carboplatinum, aminoglycoside antibiotics) as well as individuals with risk factors for ototoxicity. Risk factors include poor general medical condition with low levels of red blood cells or serum proteins (Blakley, Gupta, Myers, & Schwan, 1994); poor renal function (Forge & Schacht, 2000); co-administration of multiple ototoxic agents; age (neonates and the elderly); and heredity factors such as familial tendency for susceptibility to ototoxicity (Black & Pesznecker, 1993). Resources for identifying patients at risk include (a) medical personnel who can provide information regarding medications, patient alertness level, and availability and (b) hospital pharmacy medication lists, which provide patient names, treatment medication, and location in the hospital. Once drug therapy has been scheduled, initial contact must be made to explain purpose, benefits, and procedures involved with ototoxicity monitoring. The ability of a patient to provide reliable behavioral responses must also be determined and audiometric evaluations coordinated with the patient's availability and provider approval.

Timing of Evaluations and Testing Schedule

Ototoxicity is determined by comparing data from the Baseline Evaluation obtained prior to ototoxic drug administration to subsequent evaluations, with each patient serving as his or her own control. Evidence from animal studies suggests that ototoxicity occurs approximately 72 hours after aminoglycoside antibiotics administration (Brummett & Fox, 1982), whereas cisplatin can cause ototoxicity following a single treat-

ment (Durrant, Rodgers, Meyers, & Johnson, 1990). Based on these studies and ASHA guidelines (ASHA, 1994), the Baseline Evaluation should occur no later than 24 hours following the administration of chemotherapeutic drugs and no more than 72 hours following administration of aminoglycoside antibiotics. A recheck of thresholds within 24 hours of the Baseline Evaluation can determine patient reliability for pure-tone threshold testing.

Baseline Evaluation

Baseline Evaluations should begin with histories of medical treatment, noise exposure, tinnitus, and radiation treatment. It is essential to document concomitant ototoxic medications, noise exposure, and radiation, as they all can act synergistically with ototoxic medications. Also, any tinnitus present at baseline must be documented, as the onset of and changes in pre-existing tinnitus are potential side effects of ototoxic damage.

Full audiometric evaluations are recommended for Baseline testing of responsive patients including: otoscopy, tympanometry, acoustic reflex testing, pure-tone air and bone conduction thresholds, and speech reception and discrimination testing. The combination of tympanometry, acoustic reflex testing, and bone conduction testing can identify conductive pathologies, which confound the ototoxicity identification. Use of pulsed tones is recommended for pure-tone threshold testing, because they are easier to distinguish at high frequencies and low intensities for patients with sensorineural hearing loss and / or tinnitus (Burk & Wiley, 2004). Pure-tone testing of octave frequencies from 0.5 to 8.0 kHz (plus the interoctave frequencies 3 and 6 kHz), and of 1 / 6th-octave frequencies from 9.0 to 20 kHz is recommended. Speech audiometry (discrimination) is not a reliable indicator of ototoxic hearing loss, but is included in the Baseline Evaluation and in assessment after hearing changes are detected to aid counseling and aural rehabilitation efforts.

A shortened protocol including only the most informative tests is necessary for monitoring infants and pediatric patients with reduced attention spans and adult patients with limited response capabilities, such as those who fatigue easily, exhibit impaired orientation, or impaired alertness. Otoscopy, tympanometry, acoustic reflex testing, and objective measures of auditory function such as OAEs or ABRs should be included and will provide at least a gross measure of auditory function. Objective measures should also be included when patients with limited responsiveness become less responsive over the course of treatment.

Monitor and Post-Treatment Evaluations

Monitoring Evaluations are usually performed prior to each dose for chemotherapy patients and one to two times per week for patients receiving ototoxic antibiotics. Monitoring and appropriate referrals for further auditory and vestibular testing also are warranted any time a patient reports increased hearing difficulties, tinnitus, aural fullness, or dizziness. Confirming significant changes by retest will reduce false positive rates (ASHA, 1994). Post-treatment evaluations are necessary to confirm that hearing is stable, because ototoxic hearing loss can occur up to 6 months following drug exposure.

Monitoring Evaluations include follow-up questionnaires documenting subjective otologic complaints (tinnitus or dizziness) and the recent addition of any synergistic components (noise exposure, other ototoxic drugs, and / or radiation treatment). Audiometric tests conducted during this evaluation in alert patients are otoscopy, tympanometry, acoustic reflex testing, and pure-tone air conduction threshold testing within the SRO. If a significant pure-tone threshold change is noted, full-frequency testing should be conducted to document hearing change. If behavioral measures cannot be used, the objective measure selected for the Baseline Evaluation should be used for monitoring purposes. Middle ear dysfunction must be ruled out after changes are observed in behavioral thresholds, and ABR or OAE testing should be done to verify that changes are due to cochlear damage. The monitoring test should also be repeated on a separate day if any changes are observed. Once hearing change is confirmed, a more complete audiometric evaluation may be warranted. Frequent testing should continue until hearing has stabilized.

Post-treatment Evaluations are important for documenting significant hearing changes, identifying progressive hearing changes, and / or documenting any hearing recovery. These Evaluations should be conducted one month and 3 months after final treatment using the Monitoring procedures. Six months following cessation of treatment, a repeat of the full Baseline test battery should be completed to assess the patient's overall hearing health and determine need for further aural rehabilitation. It may be necessary to continue monitoring longer than 6 months, if hearing has not stabilized. In a longitudinal study by Bertolini and colleagues, pure-tone thresholds in young children demonstrating ototoxicity degraded further from 11% during early post-drug evaluations to 44% after 2 years (Bertolini et al., 2004).

Summary

Treatment with ototoxic medications can cause hearing loss with potential social, emotional, and vocational consequences. The early detection of ototoxic-induced hearing loss is therefore essential to patients and their health care providers, including those patients who are unable to provide reliable behavioral responses. Ototoxicity monitoring provides opportunities to consider alternative treatment regimens to minimize or prevent hearing loss progression. Audiological management of such patients can be an integral part of a therapeutic treatment plan, improving quality of life during and after treatment.

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References

ASHA. (1994). Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. *Asha, 36* (Suppl. 12), 11–19.

ASHA. (2004). *Ototoxic drugs can damage hearing.* Retrieved July 5, 2005, from www.asha.org/about/news/tipsheets/ototoxic

Barron, S. E., & Daigneault, E. A. (1987). Effect of cisplatin on hair cell morphology and lateral wall Na, K-ATPase activity. *Hearing Research, 26*, 131-137.

Beattie, R. C., Kenworthy, O. T., & Luna, C. A. (2003). Immediate and short-term reliability of distortion-product otoacoustic emissions. *International Journal of Audiology, 42*, 348-354.

Bertolini, P., Lassalle, M., Mercier, G., Raquin, M. A., Izzi, G., Corradini, N., & Hartmann, O. (2004). Platinum compound-related ototoxicity in children: Long-term follow-up reveals continuous worsening of hearing loss. *Journal of Pediatric Hematology/Oncology, 26*, 649-655.

Black, F. O., & Pesznecker, S. C. (1993). Vestibular ototoxicity. Clinical considerations. *Otolaryngologic Clinics of North America, 26*, 713-736.

Blakley, B. W., & Myers, S. F. (1993). Patterns of hearing loss resulting from cisplatinum therapy. *Otolaryngology–Head and Neck Surgery, 109*, 385-391.

Blakley, B. W., Gupta, A. K., Myers, S. F., & Schwan, S. (1994). Risk factors for ototoxicity due to cisplatin. *Archives of Otolaryngology–Head and Neck Surgery, 120*, 541-546.

Brown, J. J., Brummett, R. E., Fox, K. E., & Bendrick, T. W. (1980). Combined effects of noise and kana-mycin. Cochlear pathology and pharmacology. *Archives of Otolaryngology, 106*, 744-750.

Brummett, R. E. (1980). Drug-induced ototoxicity. *Drugs, 19*, 412-428.

Brummett, R. E., & Fox, K. E. (1982). Studies of aminoglycoside ototoxicity in animal models. In A. Whelton & H .C. Neu (Eds.), *The aminoglycosides* (pp. 419-451). New York: Marcel Dekker.

Burk, M. H., & Wiley, T. L. (2004). Continuous versus pulsed tones in audiometry. *American Journal of Audiology, 13*, 54-61.

De Lauretis, A., De Capua, B., Barbieri, M. T., Bellussi, L., & Passali, D. (1999). ABR evaluation of ototoxicity in cancer patients receiving cisplatin or carboplatin. *Scandinavian Audiology, 28*, 139-143.

Durrant, J. D., Rodgers, G., Meyers, E. N., & Johnson, J. T. (1990). Hearing loss-risk factor for cisplatin ototoxicity? Observations. *American Journal of Otology, 11*, 375-377.

Fausti, S. A., Helt, W. J., Phillips, D. S., Gordon, J. S., Bratt, G. W., Sugiura, K. M., & Noffsinger, D. (2003). Early detection of ototoxicity using 1/6th octave steps. *Journal of the American Academy of Audiology, 14*, 444-450.

Fausti, S. A., Henry, J. A., Helt, W. J., Phillips, D. S., Frey, R. H., Noff-singer, D., Larson, V. D., & Fowler, C. G. (1999). An individualized, sensitive frequency range for early detection of ototoxicity. *Ear & Hearing, 20*, 497–505.

Fausti, S. A., Henry, J. A., Schaffer, H. I., Olson, D. J., Frey, R. H., & Bagby, G. C. (1993). High-frequency monitoring for early detection of cisplatin ototoxicity. *Archives of Otolaryngology Head & Neck Surgery, 119*, 661-665.

Fausti, S. A., Henry, J. A., Schaffer, H. I., Olson, D. J., Frey, R. H., & McDonald, W. J. (1992). Early detection of aminoglycoside ototoxicity by high-frequency (³ 8 kHz) auditory evaluation. *Journal of Infectious Disease, 165*, 1026-1032.

Forge, A., & Schacht, J. (2000). Aminoglycoside antibiotics. *Audiology & Neurootology, 5*, 3-22.

Franklin, D. J., McCoy, M. J., Martin, G. K., & Lonsbury-Martin, B. L. (1992). Test/retest reliability of distortion-product and transiently evoked otoacoustic emissions. *Ear and Hearing, 13*, 417-429.

Gordon, J. S., Phillips, D., Helt, W. J., Konrad-Martin, D., & Fausti, S. A. (in press). Evaluation of insert earphones for high-frequency bedside ototoxicity monitoring. *Journal of Rehabilitation Research & Development*.

Hodges, A. V., & Lonsbury-Martin, B. L. (1998). Hearing management. In P. A. Sullivan & A. M. Guilford (Eds.), *Best practices in oncology management: Focus on swallowing and communication disorders* (pp. 269-290). San Diego, CA: Singular Press.

Lonsbury-Martin, B. L., & Martin, G. K. (2001). Evoked otoacoustic emissions as objective screeners for ototoxicity. *Seminars in Hearing, 22*, 377-391.

Roede, J., Harris, F. P., Probst, R., & Xu, L. (1993). Repeatability of distortion product otoacoustic emissions in normally hearing humans. *Audiology*, *32*, 273-281.

Rougier, F., Claude, D., Maurin, M., Sedoglavic, A., Ducher, M., Corvaisier, S., Jelliffe, R., & Maire, P. (2003). Aminoglycoside nephrotoxicity: Modeling, simulation, and control. *Antimicrobial Agents & Chemotherapy*, *47*, 1010-1016.

Simpson, T. H., Schwan, S. A., & Rintel-mann, W. F**.** (1992). Audiometric test criteria in the detection of cisplatin ototoxicity. *Journal of the American Academy of Audiology*, *3*, 176–185.

Stavroulaki, P., Apostolopoulos, N., Segas, J., Tsakanikos, M., & Adamopoulos, G. (2001). Evoked otoacoustic emissions—An approach for monitoring cisplatin induced ototoxicity in children. *International Journal of Pediatric Otorhinolaryngology*, *59*, 47-57.