American Academy of Audiology
Position Statement and
Clinical Practice Guidelines

Ototoxicity Monitoring

October 2009

AMERICAN ACADEMY OF AUDIOLOGY
www.audiology.org

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INTRODUCTION

A variety of drugs, such as certain powerful antibiotics and some anti-neoplastic drugs generally used against (potentially) life-threatening diseases can cause auditory and/or vestibular dysfunction. Auditory damage can include permanent hearing loss and tinnitus secondary to sensorineural degradation. In general the site of lesion is almost exclusively cochlear, and balance dysfunction may derive from comparable degeneration. A given drug may not have equal affinity for the two systems, hence the need to consider both. Currently, ototoxicity monitoring is most clearly established for peripheral auditory function, but there remain significant gaps in knowledge that preclude the formulation of a standard of practice in this area, per se. Yet, the existence of substantial information on ototoxicity monitoring allows: (1) evaluating the overall efficacy of current clinical methods for ototoxicity monitoring; (2) justifying inclusion of this area in the audiologist's scope of practice; and (3) developing useful ototoxicity monitoring programs for clinical and research applications. The dual purpose of this document is thus to provide a position statement on the clinical audiologist's role in ototoxicity monitoring and guidelines for the implementation of an ototoxicity monitoring program.

POSITION STATEMENT ON PROVISION OF OTOTOXIC MONITORING BY AUDIOLOGISTS

Audiological Interests in Ototoxicity Monitoring

Audiologic monitoring for ototoxicity is primarily performed for two purposes: (1) early detection of changes to hearing status presumably attributed to a drug/treatment regime so that changes in the drug regimen may be considered, and (2) audiologic intervention when handicapping hearing impairment has occurred. These clinical goals are differentiated in the following.

The term "ototoxicity monitoring" is generally taken to express the principle of early identification, yet the concept also embraces the principle of early intervention. For example, when changes are detected early, the physician can be alerted so that alternative treatment protocols, possibly with less ototoxic medications, may be considered. Furthermore, when clinically significant changes occur, especially hearing deterioration that has migrated into the speech frequencies, the purpose of a monitoring program becomes to assist the patient and/or patient's family to maintain effective communication, especially as hearing loss progresses. Unfortunately, this degree of hearing impairment may be unavoidable even with proactive ototoxicity monitoring, as the priority is effective treatment of the disease via the given drug therapy.

These two major objectives of an ototoxicity monitoring program often may create substantially different roles for the audiologist than conventional practice. Landier (1998) makes it clear that it would be advantageous for audiologists to be well aware of the same sort of considerations of the environment in which the patient is being sought and/or examined, as the logistical issues are not trivial. For example, oncology nurses are essential contact persons for the successful implementation of ototoxicity-monitoring protocols in cancer chemotherapy patients, just as recognizing key nursing personal in well-baby and newborn intensive care nurseries is essential for successful implementation of newborn hearing-screening programs. At the same time, the audiologist's native skills and talents are/should be paramount in the establishment and management of the program, including in-service education, and certainly the interpretation of results.

Once ototoxicity-monitoring protocols are established, the audiologist can accomplish the second objective of such scrutiny, that is, the management of a hearing loss that is not treatable medically. Such assistance to the patient/patient's family may include counseling, communication strategies, and prescribing amplification and/or assistive listening device(s).

Only the audiologist is endowed by their professional training with the ability to achieve both objectives of ototoxicity monitoring. The audiologist thus should take the lead in developing ototoxicity-monitoring programs, driven by the dual goals, again, of preventing or minimizing hearing loss and helping the patient to maintain the most effective hearing communication possible. These clearly are important 'quality of life' issues and quality of life is now recognized as a global imperative, whatever the medical management. Consequently, that the patient may suffer a serious and possibly life-threatening illness does not diminish the importance of these issues.

Audiologic monitoring for ototoxicity has been a very active area of research. It is outside the scope of this document to review such research, beyond that of direct topical interest. Still, it is worth concluding this section with a brief note. Namely, on-going work at a number of clinical and research centers are generating results that provide or are expected to permit comparisons among monitoring and analysis techniques for a variety of patient populations. Furthermore, new drugs are being developed that appear to have excellent therapeutic efficacy without ototoxic side effects (Campbell et al. 2003a). Still, other drugs and dietary supplements are being evaluated specifically to prevent ototoxicity when delivered either before or in combination with ototoxic drugs (see Campbell, 2007 [cf. 287-286]; Campbell et al., 2003b, 2007; Kopke et al. 1997; Sha & Schacht 2000; Doolittle et al. 2001; Blakley et al. 2002). The results of research on otoprotectants might lead to the assumption that the need for ototoxicity monitoring will disappear with effective ototoxicity prevention. It seems more likely, however, that monitoring will be essential to ensure effectiveness of such countermeasures.

CLINICAL GUIDELINES FOR OTOTOXICITY MONITORING

Major Pharmacological Agents of Interest for Monitoring and Related Issues

The most frequently used ototoxic drugs are the platinum coordination complexes, aminoglycosides, loop diuretics, and nonsteroidal anti-inflammatory agents (Humes, 1999; Garcia et al. 2001;). A summary of the bases and the nature of the ototoxic effects of these drugs is provided in the **Appendix** (page 15). Audiologists interested in establishing a monitoring program are strongly encouraged to review this material to assure a comprehensive understanding of the nature of drug ototoxicity, as well as (ultimately) the potential for the sort of protective countermeasures noted above. In practice, the audiologist is most likely to encounter ototoxic hearing loss in cases that have been treated with anti-neoplastic drugs or aminoglycosides. However, the audiologist also should be attentive to the possible toxic effects of the other classes of drugs described in the **Appendix**. For more in-depth surveys of these and various other related topics, written substantially for the audiologist, the reader is directed to Campbell (2007).

It also is important to bear in mind that ototoxic drugs may not be administered, indeed, often are not administered, in isolation, or in isolation from other effects toxic to the ear, such as other drugs, environmental toxic chemical exposures, and/or excessive noise exposure. Combined toxic effects may exceed the simple addition of individual exposure effects (i.e., nonlinear interactions may well occur) or perhaps even render a reversible effect otherwise (e.g., aspirin). Furthermore, if a localized disease process was involved in the first place as it is in most drug-treatment cases, then, it may have its own implications for audiovestibular dysfunction, and also may interact with a given drug. These effects also are summarized in the **Appendix**. In brief, the audiologist must be mindful that the disease may exacerbate the effects of ototoxic medications, which emphasizes another reason to obtain pre-treatment audiometry/audiologic data whenever possible. This also underscores the importance of the clinician's most fundamental tool--a thorough history.

It should not be assumed, additionally, that ototoxic exposure is limited to heath care. It is well known, for example, that environmental chemicals such as organic solvents, asphyxiant gases, pesticides, and heavy metals can cause hearing

and vestibular disorders (Rybak 1992; Morioka et al. 1999; Sulkowski et al. 2002; Morata 2003; Fechter et al. 2007), yet workers exposed to these agents are not monitored for ototoxicity. Ironically, some such workers may be monitored for noise induced hearing loss, yet overlooked for screening of chemical ototoxins. In clinical settings audiologists may be asked to evaluate individuals, who have had environmental ototoxic exposures. To some extent, the clinical guidelines for noise-induced hearing loss can help audiologists make decisions regarding the potential ototoxicity of exposure to an unknown chemical agent.

Similarly, ototoxicity monitoring is often not included as a part of clinical trials for new drugs, the domain of the Federal Drug Administration (FDA). Generally, the FDA only requires ototoxicity monitoring when the investigational new pharmacological agent is of a drug class known to cause ototoxicity, as a side effect. However, at this time, the FDA does not have Good Clinical Practice (GCP) guidelines for monitoring ototoxicity in clinical trials of new drugs. Yet, there are potential models in the literature. For example, Campbell et al. (2003a) reported a clinical trial of a recently developed antibiotic wherein they monitored for both cochleotoxicity and vestibulotoxicity. Their methods submitted to the FDA and approved for that study included the following procedures: air-conduction testing in the conventional and high-frequency audiometry (HFA) frequency ranges; bone-conduction testing as indicated; tympanometry and word recognition at baseline; determination of whether a significant pure-tone air conduction threshold change occurred. Patient inclusion and exclusion criteria and threshold replicability criteria were very strict to avoid false positive or negative findings. Additionally, a dizziness handicap inventory (DHI) was employed to provide, at least, a component for potentially detecting vestibulotoxicity (Jacobson & Newman 1990). The efficacy of such methods and others proposed will now be considered.

Audiological Methods Potentially of Value in Ototoxicity Monitoring

Over the past decades, three main approaches to audiologic monitoring for ototoxicity have emerged: the basic audiologic assessment, high frequency audiometry (HFA), and otoacoustic emission (OAE) measurement. They vary in utility, reliability, and purpose and applicability to specific patient populations. However, all merit consideration, depending on the goal(s) of the monitoring program. They also may be used separately or in combination. Protocol selection will be dictated by both clinical purpose and patient considerations.

First, ototoxicity monitoring tests require a baseline evaluation. Ideally, all baseline testing is performed prior to any ototoxic drug administration, so that later results have the clearest basis for interpretation. Given the high incidence of pre-existent hearing loss in the population at large, especially the elderly, the lack of a pre-treatment baseline evaluation makes it substantially more difficult to establish a clear association between the drug and a drug induced hearing loss (Campbell & Durrant 1993; Campbell et al. 2000; Campbell 2004). The baseline evaluation should include all tests that may be needed in subsequent testing, even if only a subset are used for the routine follow-up monitoring. If a change does subsequently occur on the follow-up testing, more extensive testing will be needed at that time to determine if the change is secondary to the drug, or other factors, such as otitis media, which is also common in these patient populations. Therefore, baseline testing should be fairly comprehensive and may include pure tone thresholds in the conventional frequency range, HFA, tympanometry, speech audiometry, and testing of OAEs.

The basic audiologic assessment remains an important part of ototoxicity monitoring (Campbell & Durrant 1993; Campbell 2004). However, the basic audiologic assessment, conventionally limited to frequencies of 8 kHz and below, unfortunately, does not permit the earliest detection of ototoxic changes. Yet, it is essential to the follow-up, if a change occurs and is essential for determining the patient's ability to hear speech for normal communication. The traditional basic battery, including measurement of both air and bone conduction thresholds and tympanometry, is the cornerstone of differential diagnosis, namely to rule-out an incidental conductive involvement and to assess the range of hearing most relevant to speech communication (vis-à-vis the second major goal of a monitoring program). Regarding a possible conductive component, otitis media can be common among infectious disease patients, particularly in pediatric populations

that may be receiving aminoglycoside antibiotics, or in patients immuno-suppressed by chemotherapy. Consequently, tympanometry should be performed at baseline and whenever a significant change in hearing occurs. If a sensorineural loss progresses into the conventional frequency range of 0.25-8 kHz, word recognition testing is clearly indicated and this is why word recognition, ideally, is always tested at baseline. Again, the essential element here is a basis of comparison by which to detect and evaluate any change in hearing that might occur. In some cases, an ototoxic medication may selectively cause a low- or mid-frequency hearing loss. In sum, essential to an effective ototoxicity monitoring program is, first, an effective referral system to the hearing clinic and a protocol that includes baseline testing and appropriate follow-up testing for all target patient populations. Ototoxicity monitoring thus relies ideally upon the audiologist's traditional armamentarium of tests of auditory function. On the other hand, circumstances may circumvent ideal practices and a comprehensive program requires still other approaches. Ototoxicity monitoring thus goes beyond routine clinical practice and conventional methods.

In fact, less conventional tests, such as HFA and OAE testing, have become increasingly well established for ototoxicity monitoring. In particular, such methods are more likely to be used at the first level of testing/monitoring patients treated with potentially ototoxic drugs. This is due, first, to the potential for the clinician to use such methods to detect significant change in the status of the auditory system earlier than may be possible with conventional pure tone audiometry. Second, these tests are more attractive for use in patients too ill to participate well in conventional audiometric or related methods (i.e., behavioral tests). Third, a monitoring program based upon conventional audiological assessments, particularly when administered in the clinical-laboratory setting, is not likely to be the most efficient and/or cost-effective. The test battery itself and the need to transport the patient to the optimal test environment in the audiology clinic are both time-consuming and also may not be well tolerated by an ailing patient.

High Frequency Audiometry (HFA)

The earliest effects of ototoxic drugs tend to be manifested by the outer hair cells (OHCs) of the basal cochlear turn (Fee 1980; Wright & Schaefer 1982; Schuknecht 1993). HFA comprises air-conduction threshold testing for the frequencies above 8000 Hz, ranging up to 16 or 20 kHz. HFA permits detection of aminoglycoside-induced or cisplatin-induced ototoxic losses well before changes become evident in the conventional range (Jacobson et al. 1969; Fausti et al.1984a,b, 1992c; Rappaport et al. 1985; Tange et al. 1985; Kopelman et al. 1988), because the effects of these drugs tend to first occur tonotopically basalward to the effective place limit of the conventional audiogram (Fee 1980; Wright & Schaefer 1982; Schuknecht 1993).

Although HFA was controversial for many years, it is now well established and used widely in ototoxicity monitoring programs. Still, HFA has yet to be standardized, although addressed in an "annex" (appendix) of the audiometric calibration standard (ANSI S3.6-1996). Similar methods of test administration are involved in HFA as in conventional audiometry, such as use of the modified Hughson-Westlake technique (Carhart & Jerger 1959). Hesitance to adopt HFA early on derived from concern for excessive intersubject variability of threshold measures, in part, due to the problem of standing waves in the ear canal above its resonant frequency. This anxiety has greatly diminished since the 1980's as improved instrumentation emerged. HFA thresholds were shown to be measurable with acceptable variances, and HFA was shown also to be effective for ototoxicity detection (Dreschler et al. 1985; Fausti et al. 1985; Frank 1990, 2001; Feghali & Bernstein 1991; Frank & Dreisbach 1991; Campbell et al. 2003a). Surprising, in light of the vulnerability of high-frequency hearing to the upward spread of masking and the prevalence of low frequencies in environmental noise, HFA has been shown to be efficacious in a quiet hospital room for bedside testing (Valente et al. 1992a; Gordon et al. 2005). Obtaining auditory brainstem response (ABR) thresholds at frequencies above the conventional audiogram to monitor ototoxicity bedside using a portable unit has been investigated as well (Fausti et al. 1992a,b), but has not obtained widespread clinical use. However, high-frequency ABR testing remains an area of investigation (Fausti et al. 2003; Knight et al. 2007).

However, HFA may not be applicable to all patients. Many patients with hearing loss in the conventional frequency range may not have measurable hearing at high frequencies (Osterhammel 1980; Kujansuu et al. 1989), the elderly being the most vulnerable to such exclusion (Stelmachowizc et al. 1989; Wiley et al. 1998). Any prior history of hearing loss also potentially limits the usefulness of HFA, as the most common losses are sloping high-frequency types. In these cases, hearing thresholds are expected to keep rolling off toward the upper extreme of hearing. Also, even purely NIHLs may express considerable high-frequency involvement (Fausti et al. 1981). Test efficiency is also an issue. Although audiometric inter-octave frequencies are only occasionally tested, an effective HFA test protocol is considered by some researchers/authorities (e.g., see Fausti et al. 2003) to require about as many test frequencies as conventional audiometry. Furthermore, for all the drugs in question, effects tend to be systemic (i.e., progressing from high to low frequencies) and bilaterally symmetrical. Yet, this audiometric pattern is not always the case [e.g., see Ho et al. (2007) and Huizing et al. (1987)], so both ears are routinely tested. Consequently, Fausti et al. (1992a,b, 1999) have proposed a time-efficient method for ototoxicity monitoring, based on the following considerations.

Ototoxic hearing changes tend to present first within a limited range of frequencies near the highest frequencies detected by each individual patient (Fausti et al. 1999). Consequently, most changes are observed to occur within one octave of the highest audible frequency in each patient. This range has been found to be unique for each individual and specific to the individual's hearing configuration. A shortened, serial monitoring protocol, individualized to each patient's hearing configuration thus has been proposed. A limited frequency range sensitive to ototoxic insult is defined as the highest frequency with a threshold at or below 100 dB SPL followed by the next six lower adjacent frequencies in 1/6th-octave steps, or the one octave range near the highest audible frequency. This sensitive range for ototoxicity (SRO) is determined during the baseline evaluation prior to ototoxic drug administration. Targeting the SRO for serial monitoring improves clinical efficiency by decreasing test time. A more complete evaluation is necessary if a hearing change is observed using the shortened protocol. Data obtained in the follow-up evaluation will allow hearing changes to be verified and threshold shifts due to middle ear dysfunction ruled out. Thresholds actually can be tested in 1/6th-octave steps within the SRO, whether the SRO is located above or below 8 kHz. Fausti et al. (2003) found that almost 90% of all initial ototoxic hearing changes were detected within the seven frequency SRO (Fausti et al. 2003). Thus, the shortened test protocol demonstrated a high degree of sensitivity to early decrements in hearing as a consequence of drug therapy, whether the SRO occurred within conventional audiometric frequencies or within the ultra-high frequency range (> 8 kHz). Dreschler et al. (1989) have also suggested viable abbreviated protocols.

Potential Utility of Otoacoustic Emission Testing

From the foregoing, test efficiency, per se, seems not a valid basis for excluding HFA in ototoxicity monitoring. Still, audiologists have justifiably sought other test modalities for this purpose, namely with the objectives of eliminating behavioral testing and/or achieving further improvements in test efficiency. To reiterate, drug toxicities tend to be expressed first as OHC dysfunction, and the relation of normal OAEs to intact OHCs is well established [see Robinette and Glattke (2007) for review]. The OAEs most commonly used clinically are transient OAEs (TEOAEs) or distortion product OAEs (i.e., the 2f1-f2 DPOAEs). TEOAE (Beck et al. 1992; Zorowka et al. 1993; Stavroulaki et al. 1999) and DPOAE (Muhleran and Degg 1997; Ress et al. 1999; Lonsbury-Martin & Martin 2001) responses tend to change before hearing thresholds in the conventional frequency range, but not before changes in HFA thresholds. In a study of ototoxicity monitoring in children receiving cisplatin chemotherapy, HFA usually detected ototoxic changes prior to DPOAEs, although both HFA and DPOAES changed prior to thresholds in the conventional frequency range (Knight et al. 2007). However, OAEs may still be useful as a part of an ototoxicity monitoring program, because they do not require a behavioral response and are time efficient.

An implicit issue is whether the TEOAEs and DPOAEs are equally efficacious in detecting ototoxic changes. Testing

DPOAEs may detect ototoxic change earlier than TEOAEs (Lonsbury-Martin & Martin 2001) perhaps because, practically, DPOAEs can be measured at higher frequencies than TEOAEs, thus being more sensitive to the cochlear frequency areas first affected. The DPOAEs can often be recorded in the presence of more severe sensorineural hearing loss than TEOAEs (Wier et al. 1988; Probst et al. 1991; Norton 1992) rendering more patients eligible for OAE monitoring. Detecting a change, if there is already a loss, thus is possible with DPOAE testing (see Ress et al. 1999). DPOAEs also can provide some indication of degree and configuration of hearing loss (Lonsbury-Martin & Martin 1990; Martin et al. 1990), if those data cannot be obtained behaviorally. Lastly, Arnold et al. (1999) observed cases in which a change in the high frequencies detected only by HFA had a coincidental DPOAE reduction at around 8 kHz and below. Most currently, commercially available equipment does not provide reliable DPOAE testing through the HFA test range, hence the importance of this finding. However, an approach for high-frquency DPOAE testing has been suggested by Siegel and colleagues (Siegel and Hirohata 1994; Dreisbach and Siegel 2001), but requires an additional probe microphone with tip placement deep in the ear canal. The additional instrumentation needs an extra calibration step, however, and has yet to be broadly embraced by manufacturers and clinicians alike.

Limitations of Auditory Tests

One of the primary advantages of HFA over OAE testing is that the significant change criteria for the former test are well established with excellent specificity and sensitivity [American Speec-Language-Hearing Association [ASHA) 1994]. A variety of significant change criteria have been proposed for interpretation of OAEs (Katbamna et al. 1999; Lonsbury-Martin & Martin 2001), but none yet enjoy universal acceptance. Thus, the sensitivity and specificity of these criteria need to be documented on large-scale patient populations.

As noted above, both HFA and OAE testing are problematic in patients with hearing loss, particularly in the elderly (Osterhammel 1980; Kujansuu et al. 1989; Lonsbury-Martin et al.1991; Stover & Norton 1993), because there may be no responses or limited responses available for monitoring due to pre-existing losses of OHCs in the cochlear basal region. Yet, Ress et al. (1999) found that DPOAEs could be recorded in a greater number of patients than high-frequency thresholds and were equally sensitive in detecting ototoxic change in those patients that could be tested using both measures, even if presbycusis (Rosen et al. 1964) was presumably a factor for a number of their subjects. The mean age of subjects in the latter study was 62 y.

OAE measurement in children is a particularly attractive approach for ototoxicity monitoring, namely, as an efficient objective test. Coradini et al. (2007), in fact, demonstrated the importance of incorporating OAEs--particularly DPOAEtesting in children and adolescents receiving cisplatin. Their results showed good agreement between HFA and DPOAE findings. On the other hand, as noted above, Knight et al. (2007) reported that HFA usually detected ototoxic change earlier than DPOAEs, contrary to expectations. Further, HFA is less affected by otitis media than OAEs. Otitis media is common in children and in immunosuppressed chemotherapy patients, in general, as well as in patients receiving head and neck radiation, and in patients with infections undergoing treatment with aminoglycoside antibiotics. In any event, using a test battery approach increases the chances of obtaining reliable ototoxicity monitoring data over time.

One important limitation of OAE testing as mentioned above is that the results are significantly affected by middle ear pathology such as otitis media (Allen et al. 1998). That is, OAEs are difficult to record reliably, if detected at all, in the presence of otitis media (Owens et al. 1992). And, as previously noted, the patient populations receiving ototoxic medications have increased susceptibility to otitis media, which interfere with OAE ototoxicity monitoring. For this reason alone, tympanometry, and ideally multi-frequency tympanometry, should routinely be evaluated when OAE testing is included as part of the test battery. Hence, OAE measurement probably should not be the sole method of ototoxicity monitoring, because interruptions in monitoring may occur whenever otitis media is present.

High frequency audiometry can be conducted in the presence of otitis media, but it cannot then be assumed that any changes in the HFA range are secondary uniquely to ototoxicity. Efficacious high-frequency bone conduction audiometry has yet to be developed, precluding the traditional approach to diagnostic testing, although emerging methods of testing wide-band power reflectance from the middle ear may ultimately provide a solution. At this juncture, whenever changes in any responses are noted, a complete follow-up audiologic assessment is indicated to rule out a conductive component (i.e., via conventional methods) to assure that any observed shifts are potentially attributable to ototoxicity (i.e., sensorineural loss). Clearly, using a test battery approach increases the chances of obtaining reliable ototoxicity monitoring data over time.

Other Auditory Methods and/or Issues

Tinnitus is a common side effect of many ototoxic drugs (Seligman et al. 1996), particularly cisplatin (Kopelman et al. 1988), but currently no formal tinnitus monitoring procedures have been developed. Tinnitus assessment methods are rarely reported. Sometimes tinnitus is merely analyzed via patient self-reports. Furthermore, patients with life-threatening illnesses may not self-report tinnitus, because they are overwhelmed with other issues. Whether or not tinnitus onset precedes high-frequency threshold shifts or changes in OAEs has not been investigated formally, despite the common assumption of tinnitus as an early indicator of ototoxicity. When monitoring patients for ototoxicity, questioning them systematically about any tinnitus symptoms at each appointment is strongly encouraged. For comparative information on common tinnitus questionnaires see Newman and Sandridge (2004).

The testing of auditory evoked potentials, again, is potentially attractive for ototoxicity monitoring. Fausti and his associates (Fausti et al. 2003) have invested considerable effort into working out the technical issues of stimulating and recording valid and reliable high-frequency ABRs. However, as noted previously, their methods have yet to be incorporated into manufactured evoked-potential test systems, let alone evaluated for clinical utility. Tlumak et al. (2007) reported results of high frequency stimulation of the auditory steady-state response (ASSR) for modulation frequencies at/above 80 Hz. While showing technical efficacy overall, the results were not encouraging for high-frequency electric response audiometry due to a considerably reduced dynamic range, another major challenge (in addition to the issue of standing waves) in all areas of high-frequency testing. Another consideration is that high-frequency ABR testing would be most needed in patient populations, who cannot provide reliable behavioral responses for HFA, such as young children on chemotherapy. However the use of sedation, particularly repeated use of sedation, to obtain reliable ABR recordings and track changes over time seems unadvisable and likely contraindicated because of their other health and medication issues.

Potential Bias of Noise Exposure

Eluded to earlier was the importance of querying the patient's history of noise exposure, and the issue of concomitant noise exposure is a matter that certainly warrants concern. First, the concern here is not limited to prior noise exposure. In fact, patients should always be counseled to avoid noise exposure during and for several months following (potentially) ototoxic drug administration. Aminoglycosides like gentamicin, may remain in hair cells for months after application (Aran et al. 1999). Second, as noted earlier, noise exposure can exacerbate the ototoxicity of both aminoglycosides (Dayal et al. 1971; Brown et al. 1978, 1980) and cisplatin (Sharma & Edwards 1983; Bhattacharyya & Dayal 1984; Boettcher et al. 1987; Gratton et al. 1990). In contrast to these issues, prior noise exposure has yet to be shown to potentiate ototoxicity. Laurell and Borg (1986) found no such effect in the case of cisplatin treatment, for instance. This presumably is due to the fact that the effects of overexposure to noise also tend to be expressed predominantly in the dysfunction/destruction of OHCs located more basalward along the hearing organ. Therefore, unless the ototoxic exposure dose effectively exceeds that of the prior noise exposure, further loss appears not to occur.

Vestibulotoxicity Monitoring

Although the vestibulotoxicity of some drugs, particularly certain aminoglycosides, is well established (e.g., see Seligman et al. 1996; Day et al. 2007), no widely accepted guidelines for vestibulotoxicity monitoring exist. Furthermore, some clinical vestibular tests would be impractical, if not ill-advised, for routine monitoring of this patient population. Patients of interest typically suffer malaise and have low tolerance for any discomfort that might be caused by such testing. However, there are several relatively benign instruments to help screen for balance disorders, although less-than-fully assessed for sensitivity and specificity for ototoxicity monitoring. These methods are summarized here for reference and/or for their relative ease of incorporation into a comprehensive monitoring program. Reviews of current methods for vestibulotoxicity monitoring and testing are provided by Handelsman (2007) and Black and Pesznecker (2007). General principles and clinical methods in balance assessment and rehabilitation are presented comprehensively in Jacobson and Shepherd (2008); those relevant or potentially relevant to ototoxicity monitoring are summarized briefly in the following.

Ototoxicity of the peripheral vestibular system can result in either partial or complete destruction of hair cells or deafferentation of the vestibular end organs. The functional impact of a bilateral vestibular system loss is oscillopsia during head movements and postural instability when information from the other two supporting senses, vision and somesthesia, are either absent or distorted by disease. Oscillopsia that occurs during ambulation naturally can be disorienting and destabilizing. Patients with bilateral permanent vestibular system impairments require assistive devices for ambulation. For example, in darkness, patients with bilateral vestibular system losses are at increased risk for falling. Previous investigations have documented the impact of bilateral vestibular system impairments on self-report measures of dizziness handicap. Thus, there is a critical need to monitor vestibular system function before, during, and after medical therapies that employ drugs with ototoxic properties, where it is possible and preferable to intervene (i.e., by reducing dosages or substituting less damaging medications) to stave-off permanent damage.

There are a number of possible quantitative techniques that may be used to assess vestibular system function. These include caloric testing [i.e., either bithermal, monothermal warm, or ice water caloric testing, usually referred to as electronystagmography testing (ENG)], rotational testing [i.e., either whole body, or head-only vestibular autorotation testing (VAT), vestibular evoked myogenic potentials (VEMPs), and computerized dynamic posturography (CDP)]. These methods and their clinical applications are summarized in Jacobson and Shepherd (2008).

The performance characteristics of these assessments vary. For example, caloric testing provides an assessment only of the sensitivity of the vestibular system for frequencies in the range of 0.003 Hz. “Physiological” frequencies, that is, frequencies that are encountered during normal head movements that occur in everyday life, are in the region of 1-6 Hz. However, since low frequency sensitivity is affected first by disease, the caloric test is highly sensitive to the presence of peripheral vestibular system impairment. Whole body rotational testing permits an assessment of the sensitivity and symmetry of responses of the vestibular system to higher frequencies between 0.01 Hz and 0.64 Hz. However, these frequencies still fall short of those that are encountered in everyday life. The use of the VAT provides a means of assessing frequencies that fall into the physiological range (e.g., 1 to 3-4 Hz). However, this technique has not gained wide acceptance clinically.

There are also informal or “bedside” tests that may be used to identify bilateral peripheral vestibular system impairment (Tusa 2005). These include the head-thrust and dynamic visual acuity tests. However, these informal tests are sensitive to impairments of high-frequency function. Thus, they are not helpful for the identification of the earliest signs of bilateral peripheral vestibular system impairment that begin in the lower frequencies.

Finally, there are self-report measures of dizziness disability/handicap that include the DHI noted above (Jacobson et al. 1990, 1991). The DHI, a simple paper questionnaire, may be administered, for example, at the time of audiologic assess-

ment for ototoxicity monitoring, as did Campbell et al. (2003a) in a study of a new glycopeptide antibiotic. The DHI was not initially designed for ototoxicity monitoring, but is the most commonly used and best validated self-assessment scale for dizziness and disequilibrium. However, previous investigations have shown a poor relationship between scores on self-report measures and the results of quantitative testing of the vestibular system. It is now felt that self-report measures of dizziness such as a handicap index reflect a vector of function (e.g., coping skills, anxiety, depression) that is not assessed with conventional quantitative tests (e.g., see Enloe & Shields 1997; Whitney et al. 1999; Jacobson & Calder 2000). It remains to be seen what role DHI administration can serve in this arena; still, as a quick, non-invasive, and cost-effective method of screening, it would seem worthwhile to incorporate the DHI into ototoxicity programs and thereby broadly evaluate its utility.

There is an absence of an established standard of care in vestibulotoxicity monitoring and/or a test battery well adapted to a combination of bedside evaluation and patients who often are critically ill. Therefore, a protocol should be suggested for patients who are able to be transported and who do not have intravenous lines that must remain active. It is recommended that monitoring consist of both ENG or videonystagmography testing and comprehensive rotational testing (i.e., including the frequencies 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, and 0.64 Hz). Such testing is strongly recommended for patients who in any way self-report or demonstrate signs of balance disorders in the course of treatment with known ototoxic drugs.

Adult/Geriatric Versus Pediatric Testing—Further Considerations

As summarized briefly above, both HFA and OAE testing can be problematic in patients with hearing loss developed in advance of their ototoxic exposure, and this (a priori) is the complication most common to ototoxicity monitoring in the elderly (Osterhammel 1980; Kujansuu et al. 1989; Lonsbury-Martin et al. 1991; Stover & Norton 1993). Again, Ress et al. (1999) found that DPOAEs could be recorded in a greater number of patients than those in which high-frequency thresholds fell within test limits, yet were equally sensitive in detecting ototoxic change in those patients that could be tested using both measures. As noted earlier, the mean age of subjects in their study was 62 y. Consequently, presbycusis still was likely a factor for a number of their subjects. In such cases, conventional audiometry becomes the primary monitoring tool and the focus becomes mainly one of preserving sensitivity in the speech frequencies to the extent possible, as well as management of any significantly handicapping hearing loss.

Children pose special challenges for ototoxicity monitoring. Hearing preservation is particularly critical in this patient population, because some are still acquiring speech and language. Untreated hearing impairment compromises literacy development (Yoshinaga-Itano 1999, 2003) and scholastic achievement in the years ahead (Moeller et al. 2007), as well as presenting quality of life issues that pervade all populations. These patients, especially young children, may well be too ill and/or too immature to participate well in behavioral audiometry (conventional or high frequency). Objective methods thus become essential. Otoacoustic emission testing, again, is particularly attractive, while being mindful of the complications of otitis media (Allen et al., 1998) or simply crying. Crying, in fact, precludes OAE testing (Stavroulaki et al. 1999). Frequency-specific auditory ABR testing can be used to estimate hearing thresholds in children who are too young or too ill for behavioral audiological testing. It is important to note though that high-frequency stimulus capabilities have yet to become broadly available in commercially available ABR equipment, let alone critically assessed in this population. Furthermore, sedating these ill children, who are frequently on multiple medications, may be contraindicated, particularly for repeated testing. Nonetheless, the audiologist, who is experienced in using a variety of audiologic methods, can devise appropriate patient-specific protocols, such as behavioral audiometry combined with ABR and OAE measurements, when necessary, to detect hearing loss within the conventional audiometric range. Thereafter, the audiologist is essential to comprehensive assessment and management of significant hearing loss that proves to be unavoidable. It is important to note, too, that children undergoing chemotherapy are routinely sedated for other medical procedures,

such as magnetic resonance imaging (MRI), bone marrow biopsy, and radiation. It may be possible then to coordinate a sedated ABR evaluation with these other procedure when needed.

Effective disease treatment is paramount and must be considered in program development. In adults and children alike, the approach to ototoxicity monitoring must be weighed according to clear objectives and realistic assessment of potential outcomes. Ototoxicity monitoring protocols, therefore, are somewhat disease and/or treatment specific. For example, it is well known that carboplatin is less ototoxic than cisplatin and approaches cisplatin's effectiveness as an antineoplastic treatment in some tumor types and in some patient populations. Therefore, the results of ototoxicity monitoring may help the managing physician to make decisions in choosing the course of treatment. Treatment objectives remain primary, however, and in many cases are immutable. For example, cisplatin appears to be more effective for treating certain types of tumors, such as germ cell and liver malignancies. There remains a serious lack of information on efficacy of ototoxicity monitoring and its cost-benefit ratio, however, in such cases where smaller doses or substitute treatments are implemented.

Rehabilitation is a frontier in the global issues of ototoxicity monitoring and a place where the audiologist clearly can and must play a primary role. Here, it very likely will be inadequate to assume that, after detecting significant changes in hearing and/or (especially) finding a significantly handicapping degree of impairment, management will fall into place automatically, i.e., via routine referrals to the audiologist or audiology clinics. In fact, in the backdrop of serious health conditions of the patient and just how ill the patient may be, it seems more likely that audiologic management will be only an after-thought and generally overlooked. Such under-management seems likely when one looks at the analogous relative neglect of treating other patients with serious general health problems, such as Alzheimer's disease (Durrant et al. 2005) and, in general the commonly acknowledged under-treatment of the geriatric population for hearing disorders. The impact of frequent changes in hearing status as the patient progresses through the drug-treatment protocol also needs to be considered. Ototoxicity monitoring protocols need to be more dynamic than typical clinical programs. Additionally, there are issues concerning the makeup of the treatment plan and how the costs will be covered. The latter remains a broad and dark issue of hearing health care and is beyond the scope here.

Treatment modalities are familiar—appropriate selection of assistive listening devices and/or hearing aids (presuming no medically treatable conditions, especially otitis media)—but the specifics of the case and, again, the more dynamic situation may dictate a different balance of these modalities. For example, selection of an appropriate assistive listening device might take precedence over hearing aid selection (i.e., typically the opposite of the routine management flow).

Practical Considerations for Implementation of Monitoring Program

The implementation of an effective ototoxicity monitoring program ultimately depends upon the coordination of a variety of program components, as summarized in the forgoing, and the effectiveness of audiology methods and the individual patient's circumstances. All such programs start at the level of actual audiologic testing, with critical decisions on what is to be treated as a significant change in hearing status, regardless of the particular test methods. Here, in turn, are a variety of issues.

The methods of interpretation will depend on the purpose of the monitoring. Clinically, if the purpose of the test is to detect significant ototoxic change as early as possible, the criteria developed by the ASHA (1994), as described below, are the most widely used. These criteria also work very well for HFA, which provides even earlier sensitivity to ototoxic change for those patients where HFA is appropriate. No consensus of opinion exists on significant change criteria for ototoxicity for OAEs, ABRs, or vestibular testing. For clinical trials of a potentially ototoxic drug or of an otoprotective agent, the ASHA (1994) criteria also can be used for early detection of ototoxic change. However, clinical trials generally require a grading of adverse events (AE). Although the FDA has not established GCPs for grading adverse events

in hearing, as noted above, the two most widely used adverse event scales for hearing in the literature are the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Ototoxicity Grades and Brock's Hearing Loss Grades. The NCI CTCAE ototoxicity grades for children (with adult guidelines in parentheses) are as follows

Grade 1: Threshold shift or loss of 15-25 dB relative to baseline, averaged at two or more contiguous frequencies in at least one ear (same for adults);

Grade 2: Threshold shift or loss of >25-90 dB, averaged at two contiguous test frequencies in at least one ear (same for adults);

Grade 3: Hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g., >20 dB bilateral HL in the speech frequencies; >30 dB unilateral HL; and requiring additional speech language related services) (Adults: >25-90 dB, averaged at three contiguous test frequencies in at least one ear);

Grade 4: Indication for cochlear implant and requiring additional speech language related services (Adults: profound bilateral hearing loss >90 dB HL).

Note: For children without baseline evaluation, baseline thresholds are assumed to be <5 dB HL.

The Brock's Hearing Loss Grades, which were originally designed for children receiving platinum based chemotherapeutics, are:

Grade 0: Hearing thresholds <40 dB at all frequencies;

Grade 1: Thresholds 40 dB or greater at 8000 Hz;

Grade 2: Thresholds 40 dB or greater at 4000 -8000 Hz;

Grade 3: Thresholds 40 dB or greater at 2000-8000 Hz;

Grade 4: Thresholds at 40 dB or greater at 1000-8000 Hz.

It should be born in mind that, over the years, a number of "significant change criteria" have been suggested for determination of ototoxic change. Although simple test-retest variability for each threshold should not exceed 5 dB, that criterion is too stringent for determining ototoxic threshold shift, particularly in these patient populations. Early studies of ototoxic threshold shift proposed criteria of either ≥15 dB at one or more frequencies (Thompson & Northern 1981; Reddel et al. 1982) or ≥20 dB at any one frequency. However, Brummet and Morrison (1990) reported that these criteria were exceeded even in control subjects over time. Similarly, Meyerhoff et al. (1989), in a study of patients receiving tobramycin or vancomycin, reported that 15-dB shifts at a single frequency, or average 5-dB shifts across frequencies, occurred equally in both negative and positive directions, indicating random variability.

The most widely used and validated criteria for determination of ototoxic threshold shift to date, were published by ASHA (1994) as noted above. Significant ototoxic change must meet one of the following three criteria: (a) ≥20 dB decrease at any one test frequency, (b) ≥10 dB decrease at any two adjacent frequencies, or (c) 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. It has been demonstrated that 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 (Fausti et al. 1999; Frank 2001; Campbell et al. 2003a).

Patient Identification and Testing Management

Even more fundamental to scheduling of testing is the issue of how to identify the patients to be tested and/or generate a consultation request or otherwise effectively mandate testing. In contrast to advances in newborn hearing screening, a broad mandate for the implementation of ototoxicity has yet to develop. Indeed, it seems unlikely that such a mandate will be forthcoming in the near future, considering the complex issues of how targeted patients should be identified and where/how are testing and monitoring costs are to be absorbed. These issues are likely, as well, to be highly different among medical centers' practices and the nuances of health-care practices and financing from state to state.

At this juncture, monitoring programs remain strongly dependent upon individual initiatives, although a number of references are available clearly demonstrating the overall efficacy of ototoxicity monitoring and to guide the audiologist (e.g., Campbell 2004, Fausti et al 2006). In general, the audiologist needs to develop excellent working relationships with oncologists for referrals for patients on platinum-based chemotherapeutics, and infectious-disease specialists for patients on aminoglycoside antibiotics. Although other types of drugs may be ototoxic, regularly scheduled clinical ototoxicity monitoring is usually limited to those two drug classes, as noted earlier. With modern medical database systems, it seems practical, in principle, to be able to identify efficiently those patients receiving a treatment with a potentially ototoxic drug and to target patients via automated referral generation. However, at this writing, no such system has been described in the literature.

In ototoxicity monitoring, it is essential to be proactive. To the extent possible, it is absolutely critical to obtain a baseline evaluation prior to the patient receiving the monitored drug therapy. For platinum-based chemotherapy patients, a baseline is generally possible, because the chemotherapy must be scheduled and is sometimes prescheduled in reference to associated surgical treatment. Because cisplatin can cause marked hearing loss following a single administration (Durrant et al. 1990), the importance of pre-drug baseline testing cannot be emphasized enough.

For treatment of infectious-disease patients, aminoglycoside administration may occur on an emergency basis, so prior audiologic assessment may not be feasible. Fortunately, even kanamycin, one of the most notorious aminoglycosides, generally does not cause demonstrable cochleotoxicity for at least 72 hours after administration (Brummett & Fox 1982; Brummett 1983). Consequently, baseline testing may be effectively administered within this 2-day grace period, but the efficacy of such timely testing clearly requires a highly efficient patient identification and/or referral system. It is important to note that when the desired baseline testing is not performed for the reasons described above, it could prove beneficial to ask the patient or a family member about the availability of audiometric records. Noise-exposed workers are likely, for example, to have access to such information.

Follow-up evaluations then should occur just prior to each course of platinum-based chemotherapy, after any temporary threshold shift has had time to recover, and before the patient is connected to intravenous lines or monitoring equipment. This schedule will also allow patients to be tested when they are feeling at their best, thus, providing more reliable behavioral responses. Because platinum-based chemotherapy can cause delayed or progressive hearing loss, a follow-up test should also occur a few months after chemotherapy treatment is completed. Generally this can be coordinated with a medical follow-up visit. If the patient also received head and neck radiation, monitoring for the next year or two is advisable, because hearing loss may continue to progress in such cases.

For aminoglycoside antibiotics, weekly or biweekly monitoring is recommended, ideally. Because aminoglycosides can also cause delayed hearing loss, follow-up testing should also be scheduled a few months after drug discontinuation.

Lastly, ototoxicity may occur secondary to a wide variety of agents, and monitoring protocols may need to be designed accordingly. For some drugs, the incidence of ototoxicity is so low that prospective monitoring is unlikely and yet is particularly important. The patient likely will not be referred for audiologic testing until hearing loss is suspected. Even in

cases of low-incidence drugs, the same criteria for ototoxic change are applied, but, if baseline data are not available, interpretation clearly will be problematic. As multi-drug treatments are common in the population at large, perhaps the most effective hedge against ototoxic hearing loss would be a national campaign encouraging citizens to have routine hearing checks and to maintain records thereof.

CONCLUSION

The audiologist bears the primary role in the design and development of ototoxicity monitoring programs, namely in the oversight of choice of testing protocols, patient testing or supervision of personnel administering monitoring test(s), interpretation and management of the data derived from such programs, and follow-up management when clinically significant, especially when handicapping degrees of hearing loss are detected. A variety of audiologic methods are at the disposal of the audiologist for the implementation of an effective ototoxicity monitoring program in various patient populations. They are not all "created" equally and/or are equally efficacious across the varied patient populations of potential interest. Test techniques employed and the testing schedule thus may vary according to the drug involved, the patient's age and ability to perform behavioral testing, and the purpose of the audiologic monitoring. Baseline testing is always needed to allow for adequate interpretation of the results. Careful ototoxicity monitoring can allow the physician to consider altering the treatment regimen before permanent communicative damage occurs in many cases, or allow the audiologist to work with the patient and their family to maintain communication in those cases, where hearing loss cannot be prevented or reversed. Maintaining optimal communication abilities in these patients can be a major contribution to their quality of life.

Finally, it is important to emphasize that continuing research on measurement techniques including a better understanding of sources of the responses measured and increasingly improved/optimized instrumentation holds great promise for improving the efficacy and economics of ototoxicity monitoring protocols. Similarly, such technological progress can be anticipate to lead ultimately to simpler vestibulotoxic monitoring approaches, as well as the detection of emergent hearing loss, as potentially signaled by tinnitus, which unfortunately continues to elude objective measurement. In any event, it will be essential to fully assess test sensitivity and specificity for all measures and to thoroughly assess cost-benefit parameters for the most effective monitoring program.

APPENDIX: OVERVIEW OF DRUG OTOTOXICITY

Several classes of drugs used in human medicine today are ototoxic. These drugs range from prescribed agents, such as cisplatin or many of the micin-based antibiotics, to readily available over-the-counter compounds such as aspirin. While it is not practical to give an in-depth analysis of all the classes and subclasses of drugs known to be ototoxic, it is worth reviewing a few of the most frequently used classes and underlying mechanisms of their effects on organs, such as the ear.

Platinum coordination complexes. The most successful inorganic compounds in human medicine to date are the platinum coordination complexes. These antineoplastic inorganic compounds are a vital part of the armamentarium against a variety of solid tumors. For instance, they may induce a 99% cure rate among patients suffering with testicular cancer (Giaccone 2000). Examples of platinum compounds approved for clinical use or in clinical trials are cisplatin, carboplatin, oxiloplatin, nedaplatin, ZD0473, BBR3464, and satraplatin. Cisplatin (cis-diaminedichloroplatinum–II), the

parent complex, is the most widely used and the most ototoxic drug in widespread clinical use today. At the core of the cisplatin molecule is a class B (soft) Lewis acid--platinum(II)--which is coordinated (cis) to a labile dichloride ligand and a stable di-amine. Displacement of one or both chloride ions transforms cisplatin from a neutral compound to reactive electrophiles (Lippard, 1982). These electrophilic platinum species exhibit high-binding affinity for sulfur and nitrogen-rich biomolecules (Deubel, 2004). After binding to biomolecules, the cisplatin molecule may remain reactive. For instance, after systemic treatment, intracellular cisplatin may bind sulfur to form a platinum-sulfide complex that facilitates autoxidation (Guthrie & Balaban 2004). Indeed, oxidative stress is considered a major molecular mechanism that underlies cisplatin induced cell death or apoptosis (Rybak et al. 2007). Human temporal bones harvested from patients treated with cisplatin reveal apoptosis among various cochlear cell types. Hair cells and spiral ganglion neurons are the most susceptible to apoptosis and those at the basal coil of the cochlea exhibit greater degeneration than at the apical coil (Strauss et al. 1983). These structural alterations are accompanied by reduced auditory sensitivity beginning at high frequencies and progressing to lower frequencies (Strauss et al. 1983). In addition, cisplatin damages the stria vascularis (Meech et al. 1998; Campbell et al. 1999).

Aminoglycosides. Discovered in the 1940's, aminoglycosides are the treatment of choice for tuberculosis and advanced bacterial infections (Schacht 1993). They are cost effective and therefore widely used, particularly in developing countries where the prevalence of tuberculosis has recently increased (Wu et al. 2002). Examples of aminoglycosides are: dihydrostreptomycin, tobramycin, kanamycin, amikacin, and gentamicin. Aminoglycosides contain two or more amino sugars and an aminocyclitol ring that are linked by glycosidic bonds. The molecule is non-toxic by itself, but requires the redox-capacity of a Lewis acid metal ion (Schacht 1993). Specific foci on the aminoglycoside molecule harbors soft-Lewis bases, which attracts soft-Lewis metal ions to produce (ultimately) metal complexes (Hoch et al. 1998). These complexes are redox-active and generate reactive oxygen species (ROS), which then oxidateively damage biomolecules (Jezowska-Bojczuk et al. 1998).

Hearing research has provided ubiquitous evidence for oxidative stress in aminoglycoside ototoxicity. For instance, an iron-aminoglycoside complex is believed to potentiate ROS-induced cell damage in the inner ear (Wu et al. 2002). Similar to cisplatin ototoxicity, human temporal bones reveal that various inner ear cell-types are affected by aminoglycoside treatment. However, cochlear and vestibular hair cells and neurons are the most vulnerable to cellular degeneration (Huizing & de Groot 1987; Tsuji et al. 2000). In the human cochlea, degeneration tends to begin at the basal coil and extend apically. Concommitant hearing loss thus progresses from high to low frequencies (Huizing & de Groot 1987). In the human vestibular apparatus, both type-I and II hair cells also may degenerate (Tsuji et al. 2000).

Loop diuretics. Diuretics are used to modify the composition and/or volume of body fluids to treat conditions such as hypertension, congestive heart failure, renal failure, cirrhosis, and nephrotic syndromes. Loop diuretics affect the thick ascending limb of the loop of Henle in the kidney, an organ strongly responsible for hemostasis of the blood (i.e., filtering the blood, adjusting ionic balance, etc.). The most common ototoxic loop diuretics are bumetanide (Bumex), furosemide (Lasix), and ethacrynic acid (Edecrin) (Boettcher et al. 1987). The molecular target for loop diuretics are sodium-potassium-bichloride cotransporters (Boettcher et al. 1987; Shankar & Brater 2003). Loop diuretics target proteins called soldium-potassium-2 chloride (Na+-K+-2 Cl-) cotransporters, which mediate the transfer and balance of K+, Na+ and Cl- across cell membranes (Ikeda et al. 1997). These are found in many epithelial and non-epithelial cells and have been localized in the stria vascularis of the cochlea (Hidakaet al. 1996). The inhibition of their actions results in the excretion of Na+ from the marginal cells into the intrastrial space (Higashiyama et al. 2003), demonstrating shrinkage of strial marginal cells, but swelling of strial intermediate cells and extracellular edema of the intrastrial space (see, Rybak et al. 2007). These factors can affect the endocohlear potential, which is essential to the generation of hair-cell receptor potentials of normal magnitude. Human temporal bones harvested from a patient treated with loop diurectics reveal dilation of intrastrial fluid spaces with normal hair cells and supporting cells (Arnold et al. 1981). However, dilation of the endoplas-

mic reticulum of some spiral ganglion neurons also has been observed, in which case hearing loss and vestibular hypofunction were seen.

Nonsteroidal anti-inflammatory drugs (NSAID). The most widely used over-the-counter drugs in Western societies are the NSAIDs (Boettcher et al. 1987). They are used as analgesic antipyretics, anti-platelets, anti-inflammatory agents, and in the prevention of heart attack, cerebral thrombosis, and colorectal cancer (Boettcher et al. 1987; Cazals 2000). NSAIDs are best known to inhibit the metabolism of arachidonic acid to bio-stable prostaglandins that facilitate pro-inflammatory signals. However, NSAIDs also may exhibit non-prostaglandin properties. NSAIDs are anionic planar lipophilic molecules and the lower the pH (as with increased acidity at inflammatory sites), the greater the lipophilicity. Acetylsalicylic acid (aspirin) or salicylates in general inhibit the translocation of anions across cell membranes, which may contribute to its ototoxic effect. For instance, the membrane motor protein, prestin, of the OHCs facilitates electromitility through transmembrane translocation of monovalent anions such as Cl-. Salicylate thus can inhibit electromotility (Oliver et al. 2001), thereby adversely affecting the cochlear amplifier. Human temporal bones harvested from patients treated with salycilate, nevertheless, reveal normal cochlear structures (Perez & Hayden 1968). This is consistent with the broad finding of reversibility of ototoxic effects of aspirin.

Other Considerations. As mentioned in the main text, it must be borne in mind that ototoxic drugs generally are not administered alone and may well interact with the very disease process under treatment. This line of thinking is intrinsic to concepts such as mixed antagonistic response syndromes (Ostanin et al. 2000; Werdan, 2001). When a disease process initiates local pro-inflammatory responses, as well as local anti-inflamatory responses, those processes can eventually lead to systemic spillover of inflammatory mediators. This may damage remote organs, a condition called secondary multiple organ syndrome (Davies & Hagen 1997). Recent attempts to characterize the molecular bases of secondary multiple organ syndromes have focused on NAD(P)H oxidase (NOX) enzymes. NOX enzymes may serve as pro-inflammatory mediators that increase the production of damaging ROS in remote organs due to a localized inflammation (Dorman et al. 2006). These enzymes are particularly important to audiovestibular dysfunction, because NOX3, a potent ROS generating NAD(P)H oxidase, is expressed in the inner ear at least 50 fold higher than other organs of the body, such as brain and kidney (Bánfi et al. 2004). Such heavy expression suggests that NOX3 may serve as a potent mediator of inner ear organ damage resulting from a remote disease process.

In summary, a relatively broad spectrum of ototoxic drugs and drug interactions has been identified, underlying mechanisms of their effects have been researched extensively, and ototoxicity has been increasingly well characterized in the literature. There is not only an extensive literature on histopathological and other findings in the auditory system (especially hair cells and other cochlear structures), but also on the molecular biology of events at the sub-cellular level. Such work is also shedding light on alternative treatments and even protective agents. As highly technical as the topic is and although inevitably a challenge to readers with limited relevant backgrounds, it nevertheless is useful for the audiologist to pursue at least a fundamental understanding of the basic mechanisms, as presented here. The audiologist so informed will be better prepared to interact with the medical community, as essential to a successful ototoxicity monitoring program, and to adapt to changes in health care in maintaining monitoring initiatives in the future.

ACKNOWLEDGEMENTS

The task force owes a debt of gratitude to member, Kathleen Campbell, whose scholarly book chapter (Campbell 2004) effectively and appreciably seeded this document. Work supported by the NIDCD to member Brenda L Lonsbury-Martin (with GK Martin, DC003114 and DC000613) was also cited in this statement and guidelines.

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