Chapter 12
Assessment of Interventions to Prevent Drug-Induced Hearing Loss

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Abbreviations

AAA	American Academy of Audiology
ABR	Auditory brainstem response
ASHA	American Speech Language Hearing Association
ASSR	Auditory steady state responses
CIHL	Cisplatin-induced hearing loss
DIHL	Drug-induced hearing loss
DPOAE	Distortion product otoacoustic emissions
EHF	Extended high frequency
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
IND	Investigational New Drug
IRB	Institutional Review Board
MDR-TB	Multi-drug resistant tuberculosis
NIHL	Noise-induced hearing loss
OAE	Otoacoustic emissions
OHC	Outer hair cells
TB	Tuberculosis
TEOAE	Transient otoacoustic emissions
VAT	Vestibular autorotation

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VEMP Vestibular evoked myogenic potential
VOR Vestibular-ocular reflex
WHO World Health Organization

12.1 Introduction to Ototoxicity

Many drugs used to treat disease are inadvertently toxic to the inner ear, i.e., they are "ototoxic." Drug-induced cellular impairments occur in the cochlea and/or vestibular structures and may subsequently manifest as hearing loss, tinnitus, disequilibrium, or a combination thereof. The classes of drugs which are most commonly associated with ototoxicity and/or vestibulotoxicity are aminoglycoside antibiotics, antineoplastic agents, loop diuretics, macrolide antibiotics, and antimalarials. The drugs most responsible for severe and irreversible ototoxic changes are the prescribed cancer fighting platinum-based antineoplastic agents and the powerful antimicrobial aminoglycosides (Rybak and Ramkumar 2007). These ototoxic drugs appear to preferentially affect either the cochlear or vestibular portions of the inner ear. Antineoplastics, predominantly the platinum compounds (cisplatin and carboplatin), are primarily cochleotoxic and aminoglycosides are not only cochleotoxic but are the most vestibulotoxic of all drugs depending on the specific aminoglycoside agent (Monsell et al. 1993). Of the aminoglycosides, kanamycin and amikacin are known to be exclusively cochleotoxic (Selimoglu 2007) while streptomycin and gentamicin are primarily vestibulotoxic (Schacht et al. 2012; Selimoglu 2007). Several over-the-counter medications may also become ototoxic at high cumulative dosing levels. Over 200 medications, both prescribed and over-the-counter, have been identified as potentially ototoxic. A partial list of some of these agents is listed in Table 12.1. Moreover, the ototoxic potential of several new drugs may not be fully known until widely used.

12.2 Drug-Induced Hearing Loss

Drug-induced hearing (DIHL) loss is typically permanent (although some cases are reversible), bilateral, and predominantly high frequency (Yorgason et al. 2006). DIHL is most often sensorineural and is typically secondary to the destruction of the cochlear outer hair cells (OHC) at the basal end of the cochlea, where high frequency sounds are encoded (Fausti et al. 1984a, b). The onset of ototoxic changes can be highly variable depending upon the pharmaceutical agent. Some ototoxic changes with cisplatin therapy occur very quickly, after only a single dose (Domenech et al. 1988), while both aminoglycoside and cisplatin therapy may cause delayed or progressive hearing loss months after drug discontinuation (Bertolini et al. 2004). Delayed ototoxicity may be, at least in part, related to the slowed clearance of some medications (i.e., antineoplastics and aminoglycosides)

Table 12.1 A partial list of ototoxic medications (adapted from the AAA (2009); Rybak (1986); Physician's Desk Reference (2013))

Antineoplastics	Aminoglycosides	Loop diuretics	Antimalarials	Macrolides	NSAIDS
Carboplatin	Amikacin	Azosemide	Chloroquine	Azithromycin	Aspirin
Cisplatin	Dihydrostreptomycin	Bumetanide	Chloroquine phosphate	Erythromycin	Etodolac
Nedaplatin	Gentamicin	Ethacrynic acid	Hydroxychloroquine		Fenoprofen
Oxaliplatin	Kanamycin	Furosemide	Quinacrine hydrochloride		Ibuprofen
Satraplatin	Netilmicin	Piretanide	Quinine sulfate		indomethacin
Vinblastine	Tobramycin	Torsemide			Naproxen
					Piroxicam
					Sulindac

from the inner ear fluids after the cessation of drug therapy (Li and Steyger 2009). The degree of hearing loss can widely vary even for the same agent and dosing (Fausti et al. 1984a, b). However, with prolonged administration or decreased clearance from cochlear fluids, OHC damage may spread from the apical high frequency area of the cochlea towards the basal low frequency end (Schacht et al. 2012), ultimately negatively impacting word recognition (Fausti et al. 1999).

The factors which contribute to the potential for ototoxic changes are the administration of concomitant medications (especially other ototoxic medications), dosage, age, hydration status, and individual genetic susceptibility to ototoxicity (Konrad-Martin and Keefe 2005). Ototoxic changes secondary to drug administration may be significantly exacerbated by exposure to noise (Li and Steyger 2009; Schacht et al. 2012). That is, the administration of ototoxic drugs may not only cause hearing loss but may also render the cochlea more susceptible to additional noise-induced hearing loss (NIHL) (Schacht et al. 2012). As for drug-induced vestibulotoxicity, oscillopsia, and disequilibrium, these conditions usually manifest from cellular damage which typically occurs in the macula of the saccule and/or crista ampullaris of the cochlear semicircular canals (Carey 2004). In fact, gentamicin is so well known for its damaging effects on the human vestibular system that it is intentionally administered transtympanically to ablate vestibular function in patients with severe unilateral dysfunction in order to ease their vertiginous symptoms (Nedzelski et al. 1993).

12.3 Ototoxic Medications

12.3.1 Aminoglycosides

Although many new antibiotics preclude the need for the administration of ototoxic aminoglycosides for many infections, aminoglycosides are still in common clinical use to treat serious Gram-negative aerobic bacterial infections when other antibiotics are ineffective or the patient is allergic to them (Yorgason et al. 2006). Although aminoglycosides are broad spectrum antibiotics (Schacht et al. 2012), they are not typically used to treat Gram-positive infections because alternate antibiotics with less toxic side effects are available for treating these infections in the United States. However, aminoglycosides are used routinely in the United States and globally for the management of acute infections common in cystic fibrosis patients (Prayle and Smyth 2010) as well as patients with multi-drug resistant tuberculosis (MDR-TB). In the United States, aminoglycosides are used as the last line of defense against some infectious diseases because they are stable against resistance when compared to other classes of antibiotics (Bassetti and Righi 2013). However, use is more widespread in developing countries.

The largest use of aminoglycosides occurs in developing countries because of their low cost (Chen et al. 2007), widespread availability, and effectiveness in the treatment of MDR-TB (Duggal and Sarkar 2007). With the World Health

Organization (WHO) reporting that one-third of the world's population is presently infected with the TB bacterium, global aminoglycoside use has become extensive and the numbers of those infected are expected to steadily increase over time (WHO 2009, 2010). Therefore, the incidence of aminoglycoside ototoxicity is also expected to increase among those treated for MDR-TB worldwide. In the absence of ototoxicity monitoring programs in most of these countries, incidence data are currently unavailable for many sites. However, Seddon et al. (2013) reviewed results from 35 studies of ototoxicity for MDR-TB worldwide and reported varying incidences ranging from 2.1 to 61.5 % depending on treatment regimen and definition of ototoxic change. In South Africa, where high-dose aminoglycosides are routinely used for MDR-TB, Harris et al. (2012) reported a 58 % incidence of ototoxic hearing loss with the majority being severe to profound. DIHL from aminoglycoside treatment is also considered to be a significant factor contributing to treatment noncompliance in these developing countries (Duggal and Sarkar 2007).

12.3.2 Cisplatin

Cisplatin (CDDP), the original platinum-based chemotherapeutic, has been effective in treating soft tissue neoplasms since first approved by the FDA (Platinol®, Bristol–Myers Squibb) for cancer treatment in the late 1970s (Blakley et al. 2002). The cancer types most often treated with cisplatin include ovarian, testicular, cervical, head and neck, lung and bladder (Rybak et al. 2007) in adults and osteosarcoma, neuroblastoma, hepatoblastoma, and germ-cell tumors in children (Langer et al. 2013). Although cisplatin typically provides powerful antitumor efficacy it also has been found to induce serious side effects such as sensorineural hearing loss, nephrotoxicity, neurotoxicity, and tinnitus (Adams et al. 1989; Blakley et al. 2002; Barabas et al. 2008). While researchers have found ways to circumvent the nephrotoxic side effects of cisplatin (Muraki et al. 2012), to date, no proven treatment has been found to prevent cisplatin-induced neurotoxicity and ototoxicity.

The incidence of cisplatin-induced hearing loss (CIHL) has been reported to highly vary in both adults and children receiving cisplatin therapy. The wide range of CIHL incidence variability for adults is largely due to differences in cumulative dosage, duration of treatment, types of assessments used to measure ototoxicity, and the scales used to rate the severity of ototoxicity. For children, an additional contributing factor to the high variability is the difficulty in assessing hearing thresholds in pediatric cancers that affect very young children (Brock et al. 1992). The median age of patients with neuroblastoma and hepatoblastoma is less than 18 months (Brock et al. 1992), an age range that can be challenging to obtain accurate hearing threshold assessments even among healthy children. The incidence of tinnitus is less well documented in adults receiving cisplatin therapy and is very difficult to assess in young children. Overall, the side effect of CIHL is of great concern in both the adult and pediatric populations undergoing cisplatin treatment. However, the

pediatric population is at greater risk for CIHL as Li et al. (2004) have reported that children younger than 5 years of age were 21 times more likely to develop significant hearing impairment when compared to older children (15–20 years).

12.4 Mechanisms of Ototoxic Medications

Because DIHL is typically irreversible, prevention is currently the best option available. Although the preservation of life is the principle goal with any drug treatment, a patient's quality of life should also be a fundamental consideration (Fausti et al. 2005; Duggal and Sarkar 2007). A better understanding of the mechanisms by which DIHL occurs at the cellular level has led to the development of several potential pharmacological agents for the protection of the inner ear from drug-induced damage. As reviewed in Chap. 10 by Rybak (aminoglycoside antibiotics) and Chap. 11 by Laurell (cisplatin), experiments in animal models have shown that after ototoxic drug administration, free radical formation occurs in the cochlea causing irreversible damage (Lee et al. 2004). This finding has led to proposed treatments with antioxidants to combat free radical formation and subsequent hearing loss in humans (see review by Campbell and Le Prell 2012; see also Chaps. 11 and 12 in this edition). Translational research investigations with prospective otoprotective pharmacological agents are currently in varying stages of preclinical and clinical development. However, none of these agents have yet completed the lengthy FDA clinical trial process and therefore, no agents are presently FDA approved to prevent and/or treat DIHL, tinnitus, and vestibular disorders as of the time of the writing of this chapter. The otoprotective agents that have been or are currently (as of January 2014) in various phases of clinic trials for DIHL (www.clinicaltrials.gov) (Table 12.2) are: D-methionine (Phase 2), Ebselen (Phase 2), *N*-Acetylcysteine (Phase 3), Sodium Thiosulfate (Phase 3), Amifostine (Phase 2).

12.5 Potential Otoprotective Agents

While some guidance exists for monitoring ototoxicity in patients (ASHA 1994; AAA 2009) no formal consensus exists for determining efficacy of a protective agent against ototoxicity in clinical trials. The procedures for assessing efficacy may vary somewhat depending on the ototoxin and the protective agent. For example, some studies may wish to address vestibular disorders or tinnitus in addition to hearing threshold shift. Further, the procedures may vary for Phase 1 clinical trials which focus on safety (Campbell et al. 2003), Phase 2 trials (therapeutic exploratory) which focus on safety and efficacy in a small group of volunteers (generally fewer than 100), and Phase 3 (therapeutic confirmatory) clinical trials which focus on safety and efficacy in large populations (100–1,000 s). Clinical trials for otoprotective agents against DIHL can be further complicated in that they must ensure that

Table 12.2 A list of interventional clinical trials for potential otoprotective agents (retrieved January 2014 with the search term "ototoxicity")

Agent	NCT number	Current clinical trial title	Phase	Sponsor	Status
Sodium thiosulfate	NCT00716976	Sodium thiosulfate in preventing hearing loss in young patients receiving cisplatin for newly diagnosed germ cell tumor, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy	Phase 3	Children's Oncology Group	Active, not recruiting
Sodium thiosulfate	NCT01369641	The effect of sodium thiosulfate eardrops on hearing loss in patients who receive cisplatin therapy	Not known	Thomas Jefferson University	Terminated
Sodium thiosulfate	NCT00652132	Cisplatin with or without sodium thiosulfate in treating young patients with stage I, stage II, or stage III childhood liver cancer	Phase 3	Children's Cancer And Leukaemia Group	Unknown
Sodium thiosulfate	NCT00983398	Melphalan, carboplatin, and sodium thiosulfate for patients with central nervous system (CNS) embryonal or germ cell tumors	Phase 1 Phase 2	OHSU Knight Cancer Institute	Currently recruiting participants
Sodium thiosulfate	NCT00075387	Treating patients with high-grade glioma with IA carboplatin-based chemotherapy, with or without sodium thiosulfate	Phase 2	OHSU Knight Cancer Institute	Recruiting
Sodium thiosulfate	NCT00074165	Treating patients with recurrent PCNSL with carboplatin/BBBD and adding rituxan to the treatment regimen	Phase 2	OHSU Knight Cancer Institute	Terminated
Amifostine	NCT00003269	Amifostine followed by high-dose chemotherapy in treating patients with hematologic cancer or solid tumors	Phase 2	Scripps Health	Completed
N-acetylcysteine	NCT01271088	Protective effect of N-acetylcysteine against from ototoxicity	Phase 2 Phase 3	TC Erciyes University	Completed
N-acetylcysteine	NCT01131468	Prevention of drug-induced ototoxicity in peritoneal dialysis patients by N-Acetylcysteine	Phase 2	TC Erciyes University	Completed
N-acetylcysteine	NCT01138137	N-acetylcysteine given IV with cisplatin and paclitaxel in patients with ovarian cancer	Phase 1	OHSU Knight Cancer Institute	Suspended participant recruitment
Ebselen	NCT01451853	SPI-1005 for prevention and treatment of chemotherapy-induced hearing loss	Phase 2	Sound Pharmaceuticals, Incorporated	Not yet recruiting
Ebselen	NCT01444846	Otoprotection with SPI-1005 for prevention of temporary auditory threshold shift	Phase 2	Sound Pharmaceuticals, Incorporated	Ongoing, but not recruiting

the otoprotective agent does not interfere with the intended therapeutic action of the ototoxic drug under study.

Another consideration is whether the proposed otoprotective agent is for prophylaxis and, if so, if it can be given before the ototoxic drug only or if it must be continued during and/or after the therapeutic drug is administered. Some otoprotective agents are being developed as rescue agents which means they are administered after the ototoxic event but before irreversible damage has occurred. Thus, the timing of ototoxicity testing must be carefully considered not only relative to the anticipated ototoxicity of the ototoxic drug but also relative to the anticipated protective action of the otoprotective agent. Further, because some ototoxic drugs such as aminoglycoside antibiotics (Seddon et al. 2013) and cisplatin can cause progressive hearing loss after drug discontinuation (Yasui et al. 2013), some longer time points to determine if the otoprotective agent also prevents later hearing loss progression may be optimal in the clinical trials populations. Longer time points may also be needed to ensure that the otoprotective agent does not inhibit any long-term treatment benefit of the therapeutic drug such as tumor progression or recurrence as in the case of cisplatin. Given this latter long-term safety issue, the ethics of any study that does not include the possibility for long-term follow-up must be carefully considered. Long-term follow-up will be difficult, if not impossible, for many patient populations, especially in developing countries where patients may travel long distances for treatment and monitoring.

The drug delivery method for the otoprotective agent may also influence clinical trial study design and thus sample size. For example, an otoprotective agent delivered transtympanically may allow for the opposite ear of the same subject to be used as a control while that within-subject study design would not be possible for an otoprotective agent delivered systemically.

In general, clinical trials of otoprotective agents for NIHL may be progressing more quickly than for DIHL, at least in part, because for NIHL there is no risk that the otoprotective agent will reduce the therapeutic action of a target drug. Further, the clinical trial populations for prevention of NIHL are generally relatively young and healthy. This contrasts with the less healthy patient populations receiving cisplatin chemotherapy or aminoglycoside antibiotics, who also tend to be distributed preferentially among pediatric and geriatric populations in developed countries.

Interestingly, many, but not all of the otoprotective agents being developed to prevent or rescue from NIHL, show some promise for preventing DIHL so at least some of the clinical safety data from otoprotection for NIHL clinical trials may speed development of clinical trials for otoprotection from DIHL. An Investigational New Drug application (IND) to the US Food and Drug Administration (FDA) requires two species pharmacokinetic and two species toxicology studies in Good Laboratory Practices (GLP) laboratories, and may require genotoxicity studies (FDA 2007). However, once these data are collected and reviewed, they may also serve for future studies of the same otoprotective agent for other applications. Also, Phase 1a (safety evaluation in normal human volunteers) data may also translate across studies.

Eventually, we may have the opportunity to perform clinical trials for agents that reverse long standing hearing loss by regenerating cochlear hair cells, but these agents do not appear to be on the immediate horizon clinically (Collado et al. 2008; Groves 2010). The following are some pharmacologic otoprotective agents that have been in or are approaching FDA clinical trials for protection from drug-induced ototoxicity. Clinical trials allowed to move forward by the FDA are required to be posted on www.clinicaltrials.gov. That listing allows patients to volunteer to participate in clinical trials that are in progress and can provide scientists and clinicians with the opportunity to review some aspects of study design for otoprotection clinical trials. Several agents currently in clinical trials are described below.

12.5.1 D-Methionine

D-methionine, the optical isomer of L-methionine, has been found to be protective against the ototoxic effects of antineoplastics (cisplatin and carboplatin) (Campbell et al. 1996, 1999, 2007; Lockwood et al. 2000) as well as aminoglycosides (Sha and Schacht 2000; Campbell et al. 2007) in animals. Protection against cisplatin-induced hearing loss has also been described in humans (Campbell et al. 2009). Data from animal models indicate that D-methionine does not interfere with either the antitumor effect of cisplatin (Cloven et al. 2000) or the antimicrobial action of aminoglycosides (Sha and Schacht 2000).

D-methionine has been effective when administered by intraperitoneal injection, as a pulmonary inhalant, applied directly to the round window, or consumed as an oral suspension (Campbell et al. 1996, 1999, 2007; Korver et al. 2002; Grondin et al. 2013). Having multiple options for different delivery methods can be advantageous in that round window membrane administration may avoid any possible interference with the ototoxic drug's therapeutic effect but precludes any systemic protection from other side effects (e.g., cisplatin-induced peripheral neuropathy). However round window membrane administration may not be practical on a daily basis such as for NIHL or for patients with infectious disease being treated with aminoglycosides who are more likely to have otitis media. Oral administration is generally less expensive, easier, may allow for self-administration and provides the potential of systemic protections. D-methionine is currently in Phase 3 clinical trials (NCT01345474) with the US Department of Defense to prevent permanent NIHL. One Phase 2 clinical trial to prevent cisplatin-induced hearing loss has been completed and further Phase 2 studies for both cisplatin-induced and aminoglycoside-induced hearing loss are planned. Currently oral D-methionine administration is planned for all our clinical trials.

12.5.2 *Ebselen*

A Phase 1 safety study was completed (Lynch and Kil 2009), and now Ebselen is currently in Phase 2 clinical trials to assess potential prevention temporary noise-induced threshold shift (NCT01444846). Several preclinical studies have demonstrated ebselen protection from cisplatin-induced ototoxicity as a single agent (Rybak et al. 2000) or in combination with allopurinol (Lynch and Kil 2005) although not all studies have shown significant ebselen protection from cisplatin-induced ototoxicity (Lorito et al. 2011). Baldew et al. (1990) reported that ebselen did not interfere with cisplatin's antitumor action against MPC 11 plasmacytoma or Prima breast tumor in BALB/c mice. Clinical trials for prevention of cisplatin-induced hearing loss are posted on www.clinicaltrials.gov (see Table 12.2).

Takumida et al. (1999) reported that ebselen also reduced gentamicin-induced ototoxicity in guinea pigs but reportedly no clinical trials for prevention of aminoglycoside-induced hearing loss have been registered on clinicaltrials.gov. Like D-methionine, ebselen can be administered by injection (Rybak et al. 2000) or orally (Lynch and Kil 2005). Currently, all planned clinical trials are for oral administration.

12.5.3 N-*Acetylcysteine*

N-Acetylcysteine has been studied in clinical trials to prevent NIHL but without significant otoprotection (Kramer et al. 2006; Toppila et al. 2002). Lin et al. 2010 reported some protection from temporary threshold shift depending on genetic profile of the workers.

In an early preclinical study, *N*-acetylcysteine was reported to exacerbate aminoglycoside-induced ototoxicity in the guinea pig (Bock et al. 1983). However, in two human studies, *N*-acetylcysteine has been reported to reduce aminoglycoside-induced ototoxicity (Feldman et al. 2007; Tokgoz et al. 2011). Clinical trials for prevention of aminoglycoside-induced ototoxicity are ongoing (see Table 12.2).

Transtympanic injections of *N*-acetylcysteine to prevent cisplatin-induced hearing loss yielded variable results in two clinical trials (Riga et al. 2013; Yoo et al. 2014). Riga et al. (2013) reported statistically significant *N*-acetylcysteine otoprotection for the frequency of 8,000 Hz using the patient's contralateral ear as a control. Yoo et al. (2014) reported that 2 out of 11 patients demonstrated *N*-acetylcysteine protection from cisplatin-induced ototoxicity but group results did not reach statistical significance.

Although *N*-acetylcysteine can be administered either orally (Feldman et al. 2007) or transtympanically (Riga et al. 2013; Yoo et al. 2014) the transtympanic route may be used to avoid any possible interference with the therapeutic action of the ototoxic drug, e.g., cisplatin. Further clinical trials are listed on clinicaltrials.gov (Table 12.2) for both cisplatin and aminoglycoside otoprotection.

12.5.4 Sodium Thiosulfate

Sodium thiosulfate has been studied for decades as a potential otoprotective agent for cisplatin- and carboplatin-induced ototoxicity (Otto et al. 1988; Neuwelt et al. 1996); also see Table 12.2. Clinical trials for otoprotection from platinum-based chemotherapy are ongoing as listed in www.clinicaltrials.gov. Sodium thiosulfate has not been found to prevent NIHL (Pouyatos et al. 2007) or gentamicin-induced hearing loss (Hochman et al. 2006) in preclinical studies, thus sodium thiosulfate clinical trials for otoprotection are currently focusing on chemotherapy otoprotection.

One consideration for sodium thiosulfate as an otoprotective agent is its action as a cisplatin neutralizer when given simultaneously with platinum-based chemotherapeutics (Church et al. 1995; Jones et al. 1991). Consequently, sodium thiosulfate otoprotection protocols have been designed using delay of the sodium thiosulfate administration by several hours after cisplatin administration to provide otoprotection without antitumor interference (Muldoon et al. 2000; Harned et al. 2008). Sodium thiosulfate cisplatin otoprotection has been reported by parenteral administration including injection, intravenous or intra-arterial administration. An oral formulation is available and has been used for other purposes (AlBugami et al. 2013). Several clinical trials for sodium thiosulfate are listed on www.clinicaltrials.org.

12.5.5 Amifostine

Clinical trials with amifostine have not demonstrated significant efficacy in preventing or reducing cisplatin-induced hearing loss, according to a meta-analysis across multiple clinical trials (Duval and Daniel 2012). Currently, it is not recommended for either otoprotection or neuroprotection by the American Society of Clinical Oncology 2008 Clinical Practice Guideline Update Use of Chemotherapy and Radiation Therapy Protectants American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants (Hensley et al. 2009). However, it is included in one clinical trial as a secondary end point on clinicaltrials.gov.

12.6 Monitoring for Drug-Induced Hearing Loss

12.6.1 Why and Who Should Monitor?

Formal audiological monitoring during known ototoxic drug administration is vital to detect drug-induced cochlear or vestibular changes clinically. Early detection of ototoxic changes provides the opportunity to consider possibly modifying the course of treatment to reduce these side effects or their progression.

Ototoxicity monitoring is also essential in clinical trials with new drugs that have ototoxic potential and in assessing new otoprotective agents to prevent or treat drug-induced hearing loss. Because ototoxic drugs can first cause subtle hearing changes, patient self-report or informal testing (e.g., tuning forks, watch tick, finger rub) are not sufficient for detecting drug-induced ototoxicity or for pharmacologic protection from drug-induced ototoxicity.

Because intersubject variability for DIHL is high, a priori decisions will need to be clear in the clinical trial design regarding when and if hearing loss changes will result in a subject being discontinued from the clinical trial. Although, no separate formal approved guidelines exist for ototoxicity monitoring with new drugs in clinical trials, the FDA makes recommendations for appropriate ototoxicity monitoring based upon ototoxic potential on a case-by-case basis for each clinical trial. These recommendations include modifications in the protocol if adverse events involving cochlear or vestibular changes occur. Ototoxicity monitoring is also the best means to determine the outcome of clinical trials for new pharmaceutical agents specifically targeted to treat or prevent DIHL.

A successful monitoring program requires the coordination/collaboration/cooperation among the treating physicians, nurses, and the diagnostic audiologists (AAA 2009). Identifying appropriate audiologic support and standardizing the audiologic equipment, personnel, and test procedures across multiple clinical sites, particularly if multiple countries are involved, can be challenging. Hearing healthcare professional organizations, such as the American Speech Language Association (ASHA 1994) and the American Academy of Audiology (AAA 2009), have created guidelines for ototoxicity monitoring. However, no universally accepted standardized protocols currently exist to detect or measure drug-induced ototoxicity as a whole, still less for individual drug classes. At present, each medical facility that actively administers aminoglycoside or antineoplastic therapy is responsible for developing and maintaining their own ototoxicity monitoring program (ASHA 1994). The guidelines developed by the American Speech Language Hearing Association (ASHA 1994) designate the team audiologist with the responsibility for the design and implementation of a comprehensive ototoxicity monitoring program. However, in the case of an FDA-approved clinical trial, all of the clinical trial procedures must be standardized and are part of the overall IND and Institutional Review Board (IRB) documents and procedures cannot be left to individuals at each site. Many clinical audiologists will need to be trained regarding FDA data collection and reporting procedures.

12.6.2 Whom Should Be Monitored?

A major consideration in designing clinical trials to test the efficacy of a pharmacologic agent to prevent DIHL is selection of the patient population. First, a patient population with unavoidable drug-induced ototoxicity of an incidence and degree of hearing loss to test for protection must be identified. These data bases are sometimes not readily available. Other considerations will include accessibility to the subject

pool, other clinical trials they are being recruited to, and whether or not they are able to fully understand and provide written informed consent. In some cases, the patient populations' projected longevity and attrition during a clinical trial may be a factor. The testing time points for audiologic measures will need to be coordinated possibly with patient travel to the clinical area, patient travel costs, and complicated scheduling for other appointments. The clinical trial coordinators will need to work closely with the medical treatment, audiology, and clinical trial team to ensure timely and productive communication between the treating physicians, nurses, and the audiologist. Formal ototoxicity monitoring is presently recommended for patients undergoing treatment with either of the two classes of drugs known to cause severe and permanent hearing loss, the platinum-based antineoplastics (cisplatin and carboplatin) and aminoglycosides (ASHA 1994). Therefore, for pharmacologic protective agents for those two drug classes, it may be possible to coordinate audiologic testing for a protective agent with their usual and customary audiologic care. Currently, monitoring every patient exposed to a potential or low-risk ototoxic agent is neither feasible nor cost-effective clinically, and therefore audiologic testing is not generally a part of their usual and customary clinical care. However, in clinical trials that may include testing to determine if a new drug has even a low incidence of ototoxicity that determination is made on a case-by-case basis for each clinical trial.

The team audiologist(s) should take into consideration the logistics of monitoring hearing thresholds for both adults and children receiving treatment for life-threatening diseases in different environments when designing an ototoxicity monitoring program. For example, in clinical practice, sometimes "bedside" audiologic testing is requested for very ill patients. Studies have shown good test–retest reliability of EHF "bedside" behavioral audiometric threshold responses in hospital wards if appropriate earphones are utilized (Gordon et al. 2005). However, for clinical trials, standardized audiologic test methods including use of a sound treated booth with a patient that can provide reliable data will be needed.

In addition, the audiologist should also develop a comprehensive counseling and rehabilitation program for a patient when ototoxic changes occur. Although the purpose of the clinical trial will be to determine protection from DIHL, even if the protective agent is fully effective, in the placebo group some patients may be expected to develop ototoxic hearing loss during the clinical trial and the patients will require full management of their hearing loss. Until the clinical trial is unblinded, the investigators will not know which subjects are in which arm of the study, but that fact will not alter the need for management of patient hearing loss during the course of the study. The rehabilitation program should include proper education, appropriate fitting of amplification, selection of FM devices or other rehabilitative equipment as needed, or cochlear implantation if necessary. Pre- and post-treatment counseling is an essential part of an ototoxicity monitoring/rehabilitation program as the psychological impact of the combination of a life-threatening disease with the possibility of severe permanent hearing loss can be a devastating situation for a patient and their families.

12.6.2.1 Adults

Baseline Testing

Behavioral audiometric threshold measures are the "gold standard" in monitoring a patient for ototoxic changes. Ideally, a baseline or "pre-treatment" audiological assessment should be as comprehensive as allowable. Some patients may become incapacitated during the course of their drug therapy and thus unable to complete the follow-up test battery. In such cases, objective measures of audiological assessment, such as auditory brainstem response (ABR) testing or otoacoustic emissions (OAE) tests, can be implemented but without baseline data, it is difficult to track changes in these measures. Minimally, an ototoxicity protocol should include both air (from 0.25 to 8 kHz) and bone conduction hearing threshold measures, otoscopic evaluation and tympanometry bilaterally (AAA 2009). This minimal protocol provides threshold monitoring in the conventional speech frequency region to detect changes that have the greatest impact on a patient's ability to understand speech. In addition, bone conduction threshold testing and otoscopic examination along with tympanometry will help detect any middle ear problems at baseline or onset during the drug treatment monitoring period. Otitis media is a common infectious disease among patients who may be immunosuppressed from chemotherapy, especially in the pediatric population (AAA 2009). However, because drug-induced ototoxic changes begin in the ultra-high frequency range first (>8 kHz), it is ideal to include extended high frequency (EHF) monitoring (10–18 kHz) to identify ototoxic changes before they encroach upon the conventional speech frequency range (from 0.25 to 8 kHz). It is recommended that all behavioral audiometric testing be conducted in a sound treated booth/room whenever possible in order to avoid the effects of ambient room noise (i.e., hospital wards) on auditory threshold responses (ASHA 1994).

Follow-up Testing

Scheduled follow-up testing may vary based upon the ototoxic agent and the otoprotective agent used. However, the ASHA (1994) guidelines suggest that clinical follow-up testing should occur: (1) before each administration of an ototoxic agent, (2) at the end of treatment with an ototoxic agent, and (3) at least 6 months after the end of treatment. However, for a clinical trial of a potentially ototoxic drug or for an otoprotective agent, each clinical trial will have to carefully design its testing time points. Regardless of the follow-up schedule, tympanometric measures should always be repeated if any threshold changes occur in order to rule out middle ear dysfunction as the etiology for observed changes in hearing status (AAA 2009). The ASHA guidelines are for early detection of ototoxic change and are frequently used in clinical trials for that purpose. ASHA's (1994) definition of an ototoxic change is: (a) a 20 dB or greater decrease in pure-tone threshold at one frequency, (b) a 10 dB

or greater decrease at two adjacent frequencies, or (c) a loss of response at three consecutive test frequencies in which responses were previously obtained. However, if any of one of these changes occurs, additional scales are needed to grade the degree of adverse events.

A comprehensive baseline ototoxicity monitoring protocol should be easily implemented with relatively healthy adults before the commencement of drug therapy. However, during the course of drug treatment, many patients may become incapacitated and find it difficult to return or undergo subsequent follow-up testing. Furthermore, some patients may become hospitalized and require bedside evaluations in which a portable audiometer can be used if the patient is fully responsive. In these situations, ambient noise levels should always be considered as they may interfere with accurate hearing threshold results, especially for the low frequencies (Thompson and Northern 1981). Investigators need to decide in advance whether bedside data will be included as a part of their clinical trial data. For limited response or unresponsive patients, an objective measure of hearing status with OAEs testing or an ABR test may be necessary. OAE testing is utilized to determine the status of the cochlear OHCs (Kemp 2002) ABR evaluates the status of multiple levels of the afferent auditory brainstem pathways (Bachman and Hall 1998). OAE testing, which can include either transient otoacoustic emissions (TEOAE) or distortion product otoacoustic emissions (DPOAE), is a relatively quick and easy assessment but ABR testing is quite time intensive and limited to frequency analyses of only 1–4 kHz (Mitchell et al. 2004). An advantage of DPOAEs over conventional audiometry is that they appear to detect ototoxic changes before they manifest as hearing loss in the conventional frequency range; however, high frequency audiometry is still more sensitive to ototoxic change, even in children (Knight et al. 2007). One disadvantage of both OAEs and ABRs for evaluation of new otoprotective agents for DIHL is there are no standards for interpreting those data in clinical trials to determine if significant ototoxic change occurred or was prevented.

Auditory steady state response testing (ASSR) has also been investigated as a possible objective testing procedure to assess ultra-high frequency thresholds inaccessible with ABR (10–16 kHz) (Tlumak et al. 2007). However, the feasibility of utilizing ASSR for high frequency ototoxicity monitoring is questionable at this time as ASSR threshold measures have been found to significantly overestimate behavioral threshold measures at these frequency regions (Tlumak et al. 2007). The logistics of trying to incorporate and standardize otoacoustic emissions and electrophysiologic measures into a clinical trial must also be fully considered and budgeted in advance. For example in children, electrophysiologic measures may require extensive time, more complicated scheduling and in many cases sedation and a recovery room. Some of these issues may be reduced in adult subjects and patients; however, we are still left with the challenge of deciding on significant change criteria for electrophysiologic measures.

In clinical trials, while a comprehensive baseline and end of study evaluation are generally implemented, for follow-up testing during the clinical trial, only pure tone air-conduction thresholds are sometimes used with referral to a comprehensive

assessment if significant changes meeting the ASHA criteria occur at any time during the study. The ASHA criteria can be used for both conventional and high frequency audiometric ranges (Campbell et al. 2003).

12.6.2.2 Children

Behavioral audiometric threshold measures are also the "gold standard" for pediatric patients undergoing ototoxicity monitoring (Knight et al. 2007). However, with shorter attention spans and severe illnesses, it may be difficult to obtain reliable and thorough conventional threshold responses in pediatric patients (Chang and Chinosornvatana 2010). Examiners often have to rely on objective measures of threshold estimation with pediatric patients. Ototoxicity monitoring is especially critical in young children as they tend to be at greater risk for ototoxicity than adults (Schell et al. 1989). Even a mild hearing loss has been found to have a substantial impact on the development of emerging speech and language skills (Yoshinaga-Itano and Apuzzo 1998). The loss of high frequency hearing can impair a child's ability to distinguish high frequency speech sounds (s, f, th, k, p, h, sh, ch) which contribute morphological information (i.e., the sound "s" can change the meaning of a word by making it plural) for language development (Stelmachowicz et al. 2004). High frequency hearing loss also makes it difficult to hear speech at a distance and in noisy environments (Stelmachowicz et al. 2004). Although OAE measures have not demonstrated strong correlations with low frequency conventional hearing thresholds in preschool children (Dille et al. 2007), they have shown excellent correlations with high frequency thresholds (Dille et al. 2007) which are typically the frequencies most affected with DIHL.

For clinical trials of ototoxicity or protection from DIHL in children, the testing techniques for the various ages of the children involved must be carefully designed in advance so that the data obtained will be reliable and subject to statistical analyses. Different test procedures may be needed for different age ranges and capabilities.

Follow-up testing in young children in clinical trials may need to be extended to detect progressive hearing loss. Clinically in pediatric cases, post-treatment monitoring is typically extended to longer than 1 year and some ototoxicity monitoring programs continue to monitor up to 3 years post-treatment (Knight et al. 2005). In addition, hearing loss in children that was not detected during the course of treatment has been detected after the completion of ototoxic drug therapy (Bertolini et al. 2004). However, in clinical trials to test for protection from DIHL, early time points may suffice to establish efficacy in the majority of cases.

For the very young, ill or difficult to test child, the use of objective auditory testing procedures (OAEs or ABR) may be necessary (AAA 2009). In those cases, it is essential to establish baseline measures with these tools in order to detect auditory changes throughout drug treatment (AAA 2009). However, as previously mentioned one of the biggest disadvantages of objective testing procedures is that there is no clear consensus regarding which scale or definition constitutes an ototoxic change. Although the International Society of Pediatric Oncology (SIOP) convened in 2010

to create the best version of a pediatric ototoxicity scale (Brock et al. 2012), the scale created is solely based upon the evaluation of auditory threshold results obtained from conventional and extended high frequency behavioral air conduction measures. No scale, to date, has been developed to grade changes in auditory status based upon objective audiometric measures (OAE and ABR) which are common assessment procedures used to monitor fragile pediatric cancer patients unable to undergo comprehensive behavioral assessment (AAA 2009).

12.7 Measuring Ototoxicity

No standard measure of a drug-induced ototoxic change currently exists. The ASHA (1994) criteria are most often used today for DIHL ototoxicity monitoring as these guidelines are sensitive to early ototoxic changes. They are also applicable to monitoring either conventional frequency (250–8,000 Hz) or ultra-high frequency regions (>8,000 Hz). The National Cancer Institute (NCI) also established criteria for ototoxicity as part of the standard NCI assessment which is conducted to monitor adverse events during antineoplastic therapy. This standard assessment measure is known as the common terminology criteria for adverse events (CTCAE) and has undergone three version changes since its initial creation in 1988. Several other independent ototoxicity scales have also been developed and used to define and classify DIHL (Table 12.2) over the last several decades. However, to date, no consensus has been reached on a universally excepted ototoxicity grading measure. Table 12.2 illustrates the variability between the criteria for an "ototoxic change" among several validated and not yet validated grading scales which have been developed and utilized for measuring DIHL ototoxic changes since 1982.

12.7.1 Ototoxicity Grading Scales

Two types of ototoxicity scales have evolved over the last 30 years, the baseline ototoxicity scale and the absolute ototoxicity scale. Baseline ototoxicity scales evaluate hearing changes based upon a pre-treatment baseline auditory evaluation and follow-up evaluations during and after drug treatment. In contrast, absolute ototoxicity scales were developed to grade ototoxic effects in the absence of baseline audiometric measures. Absolute scales are most often utilized in pediatric ototoxicity monitoring as baseline data are often difficult to obtain but because they assume normal hearing at baseline, room for errors in interpretation can exist. The established ASHA criteria (1994) for ototoxic change are still frequently used today as they are very sensitive to early threshold changes, especially for ultra-high frequency responses. However, several other validated and invalidated ototoxicity scales have also been created and used to define and classify DIHL (Table 12.3) over the last several decades. Table 12.2 shows the variability between the criteria

Table 12.3 Ototoxicity scales used to monitor cisplatin ototoxicity

Scale	Reference	Year	Frequency not specified	<4 kHz (dB)	<3 kHz (dB)	<2 kHz (dB)	<1 kHz (dB)
The Khan Scale	Khan et al.	1982	X				
Common terminology criteria for adverse events: CTCAE version. 1 and version. 2	(NCI) National Cancer Institute	1988, 1998	X				
CTCAE version. 3 and version. 4	NCI: National Cancer Institute	2006, 2009	15–20 dB				
ASHA criteria: American Speech/Language Hearing Association	ASHA: American Speech/Language Hearing Association	1994	20 dB or greater at any one frequency; 10 dB or greater at two adjacent frequencies; loss of response at three consecutive frequencies				
WHO: World Health Organization	WHO: World Health Organization	1997		25	25	25	25
Muenster Scale	Schmidt et al.	2007		10–60	10–60	10–60	10–60
Stohr Scale	Stöhr et al.	2005		10–60	10–60	10–60	10–60
Nitz Scale	Nitz et al.	2013		20	20	20	20
Brock “88” Scale[a]	Brock et al.	1988		40	40	40	40
Brock “91” Scale[a]	Brock et al.	1991		40	40	40	
Chang Scale[a]	Chang and Chinosornvatana	2010		20	20	20	
POG: Pediatric Oncology Group Scale	Huang et al.	2002		20–40	20–40	20–40	20–40
FHL: Functional Hearing Loss Scale	Lewis et al.	2009		20	20		
SIOP[a]: International Society of Pediatric Oncology Boston Ototoxicity Grading Scale	Brock et al.	2012		20	20		

[a]Absolute scales

for an "ototoxic change" among several grading scales which have been developed and utilized for measuring cisplatin-induced ototoxic changes since the first published scale in 1982 (Khan et al. 1982).

12.8 Patterns of DIHL

The pattern of hearing loss from drug-induced damage can differ significantly from other patterns of acquired hearing losses, specifically including NIHL. The typical pattern for NIHL reveals a "noise notch" in the audiogram occurring around 4,000 Hz (McBride and Williams 2001). On the other hand, DIHL changes for cisplatin and aminoglycoside antibiotics first occur at EHF regions (~10 kHz) (Singh Chauhan et al. 2011) and progress downward as treatment continues and cumulative dose increases (Strauss et al. 1983). These EHF losses can go undetected when audiological evaluations are confined to the conventional frequency region and do not test frequencies above 8 kHz. However, most ototoxicity monitoring programs now incorporate EHF testing into their monitoring protocols. Unfortunately, ultra-high frequency testing adds significant testing time to the already fairly lengthy testing sessions and very ill patients may not have the stamina to cooperate for a full session. Also not all ototoxic drugs follow the same pattern of hearing loss. For example, difluoromethylornithine (DFMO) may cause a wide variety of audiometric configurations and hearing loss may be reversible (McLaren et al. 2008).

12.9 Monitoring Schedule

12.9.1 Baseline Testing

Baseline audiological testing should be comprehensive and conducted before the first administration of an ototoxic medication. For antineoplastics, baseline testing should be performed before treatment. However, for aminoglycosides, testing may be conducted within the first 72 h after first administration as it has been shown that cochleotoxic changes usually do not manifest until that time (AAA 2009). Scheduling and conducting audiological baseline testing can be challenging with individuals requiring aminoglycoside therapy as these drugs are most often given on an emergency basis as opposed to the planned administration of antineoplastics.

12.9.2 Follow-up Testing

Periodic audiologic re-evaluations should occur throughout the course of all ototoxic drug treatment. There are currently no universal guidelines for audiologic monitoring for specific ototoxic medications. However, for those taking aminoglycosides,

clinical guidelines (AAA 2009) recommend weekly or at least biweekly reassessments during the course of drug treatment. Follow-up treatment assessments are also recommended a few months after the drug completion due to the potential for delayed hearing loss with aminoglycoside therapy (AAA 2009). On the other hand, the ASHA (1994) guidelines are less specific but recommend that the audiologist implement monitoring intervals during drug treatment which are optimum to detect ototoxic changes based upon the ototoxic medication administered. However, ASHA (1994) does recommend immediate post-treatment assessments for all ototoxic medications. Each clinical trial will need to carefully design its time points for audiologic assessments based on the time course of the anticipated hearing loss anticipated for the drug agent in the specific population under investigation.

12.10 Drug-Induced Vestibular Toxicity

12.10.1 Vestibular Monitoring

Monitoring for drug-induced vestibular changes, like cochlear changes, has it challenges. Like DIHL, there are no universal standards for evaluating and grading drug-induced vestibular changes and a thorough monitoring protocol usually requires a battery of vestibular assessments which may be overwhelming for very ill patients. The objective vestibular assessments, such as the vestibular evoked myogenic potential (VEMP), head thrust testing, visual acuity testing, and horizontal head impulse testing can be performed at bedside, but other objective tests (i.e., the rotary chair and vestibular autorotation (VAT)) must be conducted in the laboratory and require ambulation on the part of the patient (Black and Pesznecker 2007). In addition, subjective evaluation can be made using the Dizziness Handicap Inventory (DHI), a validated 25-item questionnaire to assess the impact of a patient's vestibular symptoms on quality of life (Handelsman 2007). However, most patients with aminoglycoside-induced vestibulotoxicity will acquire bilateral deficits and most often will not display the overt vestibular symptoms of vertigo and nystagmus seen in unilateral vestibular dysfunction (Minor 1998).

Most patients who would benefit from vestibular monitoring are usually battling a life-threatening disease and will be quite fragile and possibly nonambulatory during ototoxic drug treatment. A significant portion of these patients may also be experiencing nausea and vomiting from drug treatments and cannot tolerate routine vestibular assessments which exacerbate these conditions (Black and Pesznecker 2007). Sedatives are also routinely used in the care of these patients and can mask subjective vestibular symptoms during the course of treatment with symptoms only manifesting once treatment has been discontinued and vestibular damage has already occurred (Black and Pesznecker 2007).

As with DIHL, the development of a vestibular monitoring program should be the responsibility of the diagnostic team audiologist. No consensus has been established as to which vestibular test procedures should be utilized to best monitor drug-induced

vestibulotoxicity (Handelsman 2007). As with DIHL monitoring, a test battery approach offers the most comprehensive analysis of vestibular changes during drug treatment. As for the monitoring schedule, it is recommended that vestibulotoxic monitoring include baseline assessment measures, serial monitoring throughout drug treatment and assessment at the end of treatment (Handelsman 2007).

For clinical trials, it must first be determined if vestibulotoxicity is the focus of the clinical trial or if the clinical trial of a new drug to prevent DIHL focuses on hearing alone. If the protective agent focuses on hearing preservation only, and determination of whether or not it influences vestibular status is secondary or exploratory, the DHI may provide a quick, reliable method for monitoring (Campbell et al. 2003).

12.10.2 Vestibular Management

Counseling is an important part of a vestibular monitoring program as this side effect alone can leave patients permanently disabled and unable to resume normal activities (Black and Pesznecker 2007; Handelsman 2007). Vestibular rehabilitation is recommended for all those who experience drug-induced vestibulotoxicity. Patients who acquire unilateral vestibular losses can usually benefit from adaptation exercises to improve their vestibular reflexes. However, those who acquire bilateral losses must learn substitution strategies with their other senses in order to stabilize their gaze and help them with ambulation (Minor 1998). Again, currently no clear guidelines for assessing the vestibular efficacy of an otoprotective agent in clinical trials exist, although some clinical trials have used the DHI to assess drug-induced ototoxicity (Campbell et al. 2003).

12.11 Future Outlook

The past decades have yielded marked improvements in our ability to assess ototoxic changes across a variety of patient population. Further a number of new scales for early detection of ototoxicity, and grading ototoxicity have allowed better quantification of the data and comparison across studies. The wide variety of scales being used can have the advantage of allowing the investigator to select the measure most applicable to their study population, the lack of agreement on which scales to use in similar populations renders comparisons across studies problematic. Further not all drugs affect hearing in an identical manner or across the same time course. As otoprotective agents progress through multiple clinical trials, we will need to arrive at some method for comparing the relative efficacy of these agents. Further, we need better measures for the assessment of drug-induced vestibular function.

Nonetheless, the progress has been remarkable and the current and future clinical trials for otoprotective agents against various drug-induced ototoxicities suggest

that in the future we may be able to reduce or eliminate ototoxic hearing loss in a variety of patient populations. Preserving the hearing in these patients could markedly improve their quality of life.

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