Ototoxicity

Nonclinical Evaluation During Drug Development

David Hicks and Jeremy Turner

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Abstract

Ototoxicity is the cellular degeneration of the cochlea or vestibular tissues, resulting from the exposure to certain therapeutic agents or chemicals, which typically leads to functional deterioration in hearing or balance. Common symptoms of ototoxicity include sensorineural hearing loss, hearing in noisy or complex environments, tinnitus, hyperacusis (discomfort resulting from perception of loud sounds), pressure or fullness in the ears, dizziness, and vertigo. Certain classes of medications are known to be especially likely to cause significant ototoxic damage. Routine screening of ototoxicity potential in certain classes of new drugs during preclinical development is essential.

Auditory Dysfunction and Current Treatment Options

The human ear, like that of other mammalian species, is generally divided into three anatomic regions:

- The **outer** ear: the folded auricle, the ear canal, and the tympanic membrane or eardrum
- The **middle** ear: an air-filled space containing three connected bones – the malleus, incus, and stapes
- The **inner** ear: the special sense organs of hearing (the cochlea) and balance (the utricle, saccule, and semicircular canals) which are all

D. Hicks · J. Turner (✉)
Turner Scientific, LLC, Jacksonville, IL, USA
e-mail: jturner@turnerscientific.com

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contained in dense bone. Nerves from these special sense organs, the auditory (hearing) nerve and the vestibular (balance) nerve, carry signals from the ears to the brain, and some modifying signals from the brain to the ears.

The overall hearing function of the outer and middle ears is to convert sound energy to mechanical energy, which depends on physical (mechanical) changes – each structure is basically pushing the next, causing vibrations to be transmitted in series. The inner ear, in contrast, converts these mechanical forces into electrical energy through specialized "hair cells" which generate nerve impulses. The balance organs function in a similar manner: changes in head position cause fluid to shift and hairs to bend, generating nerve impulses and giving a sense of movement or alteration in position.

Dysfunction of the outer and middle ears is generally caused by macroscopic physical changes that prevent proper movement of structures. A variety of surgical and medicinal treatment options exists to reverse this "conductive" hearing loss. Inner ear dysfunction, by contrast, often involves damage to microscopic structures like the hair cells and auditory or vestibular nerve fibers. Resulting hearing loss is known as "sensorineural." Tinnitus (ringing in the ears) can also result from either inner ear dysfunction, or in the brain as a result of decreased auditory input.

Treatment options for inner ear dysfunction are very limited. Sensorineural hearing loss is irreversible in almost all cases, as hair cells and auditory nerve fibers do not regenerate. Hearing aids can be helpful for some patients, and cochlear implantation can be considered in patients with severe to profound hearing loss. However, neither intervention truly restores normal function. There are currently no reliably effective treatments for tinnitus, although hearing aids, cochlear implants, and therapy have each shown promise in some people.

Why Hearing Is Important

It is difficult to truly appreciate the effects of hearing loss until a person experiences it. Unlike the eyes, which can simply be closed, there is no way to "turn off" the ears. It is possible, therefore, that people without hearing loss may take for granted the contributions of hearing to daily life. Hearing contributes to awareness and safety because, unlike sight, it is multidirectional and can locate the distance and direction of a threatening event, providing warnings even during sleep. Hearing is essential for satisfactory communication, as a typical person speaks thousands of words per day and hearing these words allows for understanding of ideas and emotional cues from the speaker. Hearing is also crucial for the enjoyment of life, through participating in activities that depend on sound such as listening to music and other media, or simply appreciating the richness of one's surroundings.

Consequences of Mild to Moderate Hearing Loss

Significant evidence shows that mild to moderate sensorineural hearing loss, even when compensated by hearing aids, can lead to multiple negative sequelae for both adults and children.

Consequences of mild to moderate hearing loss in adults: In medical and scientific literature, there is often an assumption that the psychosocial consequences of hearing loss on adults, such as communication difficulties, social isolation, cognitive impairment, lower wages, and depression, apply mostly to elderly adults, usually with more severe forms of hearing loss (Monzani et al. 2008). In reality, adults with mild and moderate hearing loss report many problems such as poor identity (feeling old and unintelligent), decreased participation in social activities, communication and relationship difficulties, fewer community and professional activities, and more loneliness (Heffernan et al. 2016). Other correlated events and consequences of mild to moderate hearing loss include:

- Poor cognitive function and early onset of dementia (Fortunato et al. 2016)
- Faster decline in cognitive testing scores (Lin et al. 2013)
- Higher rates of dementia (Lin et al. 2011)
- Increased relationship and professional problems among younger adults (Monzani et al. 2008)
- Increased rate of early retirement among younger individuals (Helvik et al. 2012)
- Reduced quality of life (Mulrow et al. 1990)
- Higher risk of depressive symptoms (Gopinath et al. 2009)

Consequences of mild to moderate hearing loss in children: There is significant evidence in pediatric hearing literature that shows even mild hearing loss or delayed hearing leads to high costs for children in terms of overall health, psychological wellbeing, and social integration (Bass et al. 2016). Mild to moderate pediatric hearing loss has been associated with:

- Poor academic performance (Hornsby et al. 2017), including lower scores on comprehensive basic skills tests in third grade and higher rates of failing at least one grade (Bess et al. 1998)
- Increased learning difficulty in reading, math, and general studies among cancer survivors with mild or moderate hearing loss (Gurney et al. 2007)
- Increased classroom fatigue and stress due to the increased attention and concentration needed for listening in the classroom (Hornsby et al. 2017)
- Lower observed and self-reported quality of life scores (Gurney et al. 2007)
- Greater dysfunction in terms of behavior, energy, stress, social support, and self-esteem (Bess et al. 1998)

Even as adults the consequences can be significant. Children with hearing loss are up to 39% less likely to attend college, are twice as likely to experience work stress, and have lower labor participation rates than normal hearing individuals (Roland et al. 2016).

Summary of Ototoxicity

Ototoxicity is the cellular degeneration of the cochlea or vestibular tissues, resulting from the exposure to certain therapeutic agents or chemicals, which leads to functional deterioration (Ganesan et al. 2018). Common symptoms of ototoxicity include sensorineural hearing loss, tinnitus, hyperacusis (discomfort resulting from perception of loud sounds), pressure or fullness in the ears, dizziness, and vertigo.

Certain classes of medications are known to be especially likely to cause significant ototoxic damage:

- Chemotherapeutic agents such as platinum-based anticancer medications (cisplatin). Ototoxicity rates from cisplatin use reach 90% in high-risk groups and can lead to severe hearing loss in up to 71% of patients (Landier et al. 2014).
- Certain anti-infective medications such as aminoglycosides, macrolides, vancomycin, and antimalarial treatments. Ototoxic hearing loss and vestibular dysfunction occur in approximately 20% of patients who receive aminoglycosides intravenously for multiple days (Jiang et al. 2016).
- Loop diuretics such as furosemide (Ding et al. 2016).
- Central nervous system agents such as anticonvulsants (Hamed 2017), narcotic analgesics (Ho et al. 2007), acetaminophen (Kyle et al. 2015), and NSAIDs.

More generally, ototoxic side effects are linked to many medications. The SIDER Side Effect Resource version 4.1 reports that 395 of 1430 currently marketed medications (27.6%) have the potential to cause tinnitus, 122 (8.5%) have the potential to cause hearing impairment, and 110 (7.7%) have the potential to cause deafness.

Vertigo and other vestibular disorders are linked to 508 (35.5%) of medications (SIDER 2015).

An important caveat about ototoxicity to consider when designing studies and evaluating the ototoxic potential of a chemical or new drug is to note that noise and age alone can cause similar changes, and that they can act synergistically with chemicals or drugs to exacerbate the damage. In order to properly evaluate the ototoxicity of those potential contributors, preclinical and clinical studies must be designed to carefully control for environmental noise exposure, age of the animal or human subjects, environmental/workplace chemical exposure, and drug use history. For example, it is clear that exposure to certain solvents (toluene and fuel) in a noisy environment can produce synergistic damage to the auditory system. Exposure to even moderate noise levels can potentiate both aminoglycoside and cisplatin-induced ototoxicity (Steyger 2009) and it is clear that very few preclinical or clinical studies document the environmental noise exposure experienced by their test subjects.

The Current Regulatory Environment Related to Ototoxicity

Despite the high prevalence of ototoxic side effects among presently approved drugs (described above), there is currently no recommendation that new medications be routinely screened for ototoxic potential. In 2003, at the request of the US Food and Drug Administration (FDA), the Society of Toxicologic Pathology (STP) created a recommended list of 42 core tissues to be tested histopathologically in repeat-dose toxicity and carcinogenicity studies (Bregman et al. 2003). However, the ears were the only major organ or sensory system not included in this list.

The FDA has commented in the recent past on the importance of ototoxicity screening. In a guidance document issued in 2015, it was recommended that "If [a] drug product is expected to reach the middle or inner ear during clinical use or is introduced directly to those regions, evaluation of the auditory brainstem response, as well as microscopy of relevant otic tissue, including a cytocochleogram, should be included in acute and/or repeat-dose studies conducted by intratympanic administration" (US Department of Health and Human Services, Food, and Drug Administration 2015). However, this guidance document was specific only to reformulated drug products and products for which a new otic route of administration was being evaluated. Therefore, its influence on the routine ototoxic screening of new drug products was likely minimal.

The Importance of Ototoxicity Screening

Many drug developers and regulatory experts assume that only severe consequences of ototoxicity (profound hearing loss and deafness) are worthy of preventative efforts. It is often concluded that if a drug causes mild to moderate hearing loss, this is a small and acceptable price to pay for the drug's therapeutic benefits. Additionally, it is likely that only profound consequences of ototoxicity are ever noticed. However, in reality, harm from ototoxic medications can occur gradually and thus be underappreciated.

Hearing impairment does not need to be severe to have a significantly detrimental effect on the lives of adults and children. It is therefore clear that any effective measures to prevent ototoxic hearing loss would be beneficial to cognitive function, social participation, workplace success, psychosocial health, educational success, and other measures of quality of life.

Efforts to prevent ototoxic damage would have important financial benefits. The average lifetime socioeconomic burden of hearing loss of any cause, in 2015 dollars, is estimated at $1.4 million for a prelingually deafened child, and $350,000 for each adult with acquired hearing loss. And, given the educational consequences of even mild to moderate hearing loss caused by ototoxicity, federal and state governments may be motivated to promote regulations that limit harm to the ears. In the USA, for example, under the Individuals with Disabilities Education Act, funding for

assistive hearing devices in classrooms and audiological services is required, and Individualized Educational Programs must be developed for hearing-impaired students who qualify for special education services (Bass et al. 2016). Thus, in addition to protecting the public from ototoxic drugs, governments could reduce education costs, even for students with mild or moderate acquired hearing loss, by requiring better preventative measures against ototoxicity.

The goal of ototoxicity screening need not focus only on the elimination of most ototoxic damage. Additionally, simple awareness of the potential for hearing loss, tinnitus, and vestibular dysfunction would help clinicians and members of the public to make more informed decisions about what medications are prescribed and used.

If such awareness does lead to even subtle reductions in ototoxic damage, the benefits could still be significant. For example, it is believed that a relatively small (10 decibel) improvement in hearing thresholds could make a significant difference in an individual's ability to accurately perceive the clarity of speech that he or she is hearing, especially in a noisy environment (Campbell et al. 2016). Such an improvement could allow an individual to participate in social engagements or hear the voice of a grandchild or spouse. Thus, preventing even this degree of hearing loss through ototoxic screening and awareness would be quite worthwhile.

Recommendations for Screening for Ototoxicity

Standard test battery: A standard preclinical test battery for ototoxicity should be comprehensive enough to capture a broad range of adverse effects on auditory function and anatomy, but not overly burdensome and impractical. It should also involve tests that are well accepted and relatively easy to perform:

- Physiologic testing to assess audiologic function of multiple processes and brain regions
- Histologic testing to assess microscopic anatomy of sensitive and important structures that are vulnerable to ototoxic damage

The standard preclinical test battery should include the auditory brainstem response (ABR), and histology with cytocochleogram hair cell counts and often H&E histopathology (especially when local administration is used). Increasingly there is also concern that some ototoxins may not kill hair cells but damage the auditory nerve afferent, and the ABR and histology can both be adjusted to address that concern as well. It is also possible to conduct screening for potential ototoxicity using a range of behavioral testing methods that can assess hearing loss and tinnitus (Turner 2007).

A well-designed nonclinical development program incorporating these tests will detect clear adverse effects on the auditory system. ABR and histological assessment are currently recognized by the FDA as recommended preclinical methods to assess the effect of reformulated drugs and drugs administered through alternate routes on audiologic function in acute and/or repeat dose studies (US Department of Health and Human Services, Food, and Drug Administration 2015). Given the existing ototoxic potential summarized above, we recommend such testing apply to the preclinical development of any of the following classes of medications, regardless of formulation status or administrative route:

- Chemotherapeutic (anticancer) compounds
- Anti-infective medications
- Loop diuretics
- Central nervous system agents, or any drug that is known to cross the blood-brain barrier

Additional assessments: Consider the following questions when deciding if the standard test battery for ototoxicity will provide adequate information regarding the potential of a drug to interfere with audiologic function:

- Does the chemical or drug cross the blood-labyrinth barrier? Initial cochlear pharmacokinetic data can help determine risk by assessing

whether the drug or chemical crosses the blood labyrinth barrier to reach the fluids and sensitive tissues of the inner ear.
- Is the drug likely to cross the blood-brain barrier and affect neurotransmitter systems within the brain?
- Is there evidence that the drug is affecting the ability of test animals to maintain adequate balance?
- Is the drug being administered directly into the ear canal or middle ear space?

If the answer to any of these questions is affirmative, additional assessments of audiologic function and microanatomy may be warranted.

Nonclinical study design considerations: Auditory function and anatomy are generally similar across mammalian species including humans, but age, sex, and environmental noise levels can influence the appropriateness of nonclinical study designs:

- Rodent models, such as mice, rats, or guinea pigs, should be the preferred species for ototoxicity evaluation in single-species studies.
- Both sexes should be used in nonclinical studies, as sex-related hormones can influence auditory function or interact with drug treatments differently.
- Newborn or younger animals, chosen to target the developmental period of interest, should be considered when the drug being evaluated is intended for pediatric use.
- Studies should include appropriate cohorts of control animals (negative controls that receive no treatment and/or vehicle solution of the test article). If an otic surgical administration route of the drug is required, a group of control animals that undergo this procedure without drug or vehicle administration should be included. If the drug being evaluated is similar in class to a known ototoxic medication, a group of positive control animals should be included that receives this known ototoxic medication.
- Age should be carefully controlled and reported as age can interact importantly with potential ototoxins.
- Vivarium noise levels should be monitoring and reported. This should include chronic/typical daily noise exposure levels as well as occurrence (amplitude, duration, and frequency) of acute noise exposure levels resulting from cage changing, high-pressure washing, transport of animals, etc. should be monitored and reported.

Challenges in evaluating human ototoxicity: Current drug development practices often involve ototoxic evaluation in humans only after signs and symptoms of ototoxicity have developed. There are many challenges associated with evaluating ototoxicity in humans:

- Adverse effects on auditory function may present long after use of a drug, thus making a connection between use of a drug and its deleterious effects difficult.
- Auditory function can suffer from other causes that are compounded by drug use, such as acute or chronic noise exposure or aging. Thus, while the ototoxic effects of a drug may be real, they could be erroneously attributed to other causes.
- Routine audiologic testing in humans would not be able to adequately describe the full range of effects a drug could have on auditory function, such as a relatively new phenomenon described as "hidden" hearing loss (Liberman and Kujawa 2017) whereby hair cells do not die but their auditory synaptic afferents degrade, resulting in no loss of hearing thresholds but rather loss of suprathreshold responsiveness, possibly tinnitus, and difficulty listening in complicated environments.

Conducting human clinical trials to assess ototoxicity is thus difficult, given the long duration of evaluation that would be required, the challenges of recruiting appropriate patients, and the difficulty in performing complete functional and pathologic tests. Nonclinical evaluation of ototoxicity would be able to overcome these challenges, as suggested by a recent preclinical study which demonstrated reduced evidence of hidden hearing loss caused by certain aminoglycoside antibiotics

(Ishikawa et al. 2019). Such improved toxicity would have been difficult to show in clinical trials, given the need for harvesting of tissue and technical histologic analysis.

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