Chapter 9
Vestibular Ototoxicity

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Introduction

Available evidence demonstrates that early detection of toxicity through prospective monitoring allows for treatment modifications to minimize and prevent permanent hearing loss and balance impairment. Many monitoring protocols for the prevention of ototoxicity have been described, but their practical application is difficult to implement because of several variables. Current protocols when administering potentially ototoxic agents have been shown to be effective in recognizing early ototoxicity and thus allowing for the prevention of permanent, irreversible damage [1]. Implementation of these protocols (especially protocols to evaluate the vestibular system) is frequently difficult to carry out because of the incapacitated or obtunded status of the patient. Since the patient is seriously ill, they are unable to inform their physicians that they are experiencing symptoms of ototoxicity. Thus, it is only when the patient is recovering that they are able to perceive that the medications that they have received are ototoxic. At this time, there is no consensus regarding the choice of early ototoxicity identification methodology.

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Historical Perspective

Mercury was once thought to be a cure for syphilis. Hence the axiom, "Spend a night with Venus, and you'll spend a lifetime with Mercury." In this case, the cure proved far more terrible than the disease. Treatment with mercury resulted in severe vertigo, deafness, uncontrollable tremors, and insanity.

When streptomycin was first discovered, it was thought to be a miracle cure for tuberculosis. It was soon seen that it resulted in severe cochlear and vestibular ototoxicity. This led to a search for a medication that was effective against tuberculosis but was far less vestibulotoxic. This led to the discovery of dihydrostreptomycin, which was as effective against tuberculosis but was mildly vestibulotoxic.

In the 1960s, other aminoglycosides were discovered, and it was found that they were all ototoxic, some being more ototoxic to the cochlea while others affected the vestibular system much more than they damaged the cochlea.

Subsequently, many ototoxic pharmacologic agents that are vestibular toxic have been discovered. They are loop diuretics, salicylates, quinidine, and other antibiotics, including minocycline, erythromycin, polymyxin, and chloramphenicol. Chemotherapeutic agents like cisplatin are also severely vestibulotoxic.

Epidemiology

Ototoxicity can affect all age groups. The global incidence is not known. This may be due to a variety of reasons, like the existence of varied and diverse criteria to define.

Ototoxicity There could be a wide spectrum of reactions to a known ototoxic drug in different ethnic groups. The utilization of various audiological protocols for the evaluation of ototoxicity and the lack of referral for otological symptoms could account for the absence of a true incidence of ototoxicity.

Cisplatin ototoxicity occurs in a range between 23% and 50% in adults and up to 60% in children. Some reports have found elevated hearing thresholds in up to 100% of cisplatin-treated cancer patients, while it is estimated to be 63% with aminoglycosides and 6–7% with furosemide. It should also be noted that the incidence and severity of ototoxic hearing loss appear to be dose-dependent and, at times, influenced by the cumulative buildup of ototoxic medication. Other considerations like age, gender, and comorbid conditions like congestive heart failure, renal failure, hypertension, genetic susceptibility, geographic factors, type of drug, route of administration, duration of therapy, bioavailability, and preexisting hearing loss also influence the course and severity of ototoxicity.

Pathophysiology of Ototoxicity

Animal studies have found damage to occur in the hair cells of the organ of Corti, the ampullary cristae, the maculae of the utricle, and the saccule.

Inside the vestibular receptors, the most extensive damage occurs in the apex of the cristae and the striolar regions of the maculae. As ototoxicity increases, the progression of hair cell loss is seen to extend to the periphery of the vestibular receptors. In general, it is noted that vestibular type 1 hair cells are more susceptible to damage than type 2 hair cells. Aminoglycosides have been found to cause severe damage to the otoconial membrane and otolith structures. In end-stage ototoxicity, degeneration of ganglion cells is observed.

Ototoxic medications enter the inner ear directly through intravenous injection, intramuscular injection, or topically when administered as ear drops.

Some chemical toxins and solvents enter the bloodstream through alveolar oxygen transport following inhalation of toxic fumes. How exactly these toxins enter the inner ear through the bloodstream is not clear at this time.

It has been postulated that these toxins enter the perilymph vascularis via the spiral ligament or into the endolymph via the stria vascularis.

The round window membrane is another portal of entry for toxic substances to enter the inner ear. The round window membrane acts as a semipermeable and selective membrane. Factors that affect permeability include size, concentration, electrical charge, the thickness of the round window membrane, and facilitating agents that enhance transfer to the inner ear across the round window membrane. All the morphologic evidence available for the round window membrane suggests that it participates in the resorption and secretion of substances to and from the inner ear. The round window membrane acts as an active ionic pump for substances from the middle ear into the inner ear. It is thought that the membrane could very likely play a role in the defense system of the inner ear. Various substances, like antibiotics and tracers, when placed in the middle ear, traverse the membrane. Tracers placed in perilymph become incorporated into the membrane by the inner epithelial cell membrane. Substances traverse through the round window membrane through pinocytotic vesicles.

Congenital ototoxicity can occur during pregnancy if the mother has been exposed to ototoxic agents. The ototoxic agent passes through the placenta to the developing fetus. The first trimester is the most vulnerable time for the developing fetus. In addition to the damage to the vestibular system and the cochlea, the child may be born with several birth defects as a direct consequence of being subjected to ototoxic medications.

Symptoms of Vestibular Ototoxicity

Oscillopsia due to bilateral vestibular hypofunction is a dominant symptom that occurs in vestibulotoxicity. Oscillopsia is the perception that stationary objects or surroundings move coincidentally with head movement, resulting in dizziness, motion sickness, and unsteadiness when standing or walking, especially in the dark.

With oscillopsia, illusory movements occur on the same plane as head movement but in the opposite direction. This usually gives the patient the impression that the environment is whirling around. This results in dizziness, motion sickness, and unsteadiness, especially when standing or walking. This worsens in the dark, where there are no visual cues to guide the patient.

Unsteadiness when standing or walking can range from mild to severe, depending on the severity of the vestibular loss. Most patients with bilateral vestibular loss are completely dependent on visual and somatosensory input in order to maintain posture control. Therefore, disorders that adversely impact the function of one or both of these systems will have a greater negative functional impact.

While it would be logical to assume that systemically administered medications would affect both ears equally, this has not always been true—vestibulotoxicity can also be unilateral or asymmetrical. Unilateral vestibular paresis, or non-lateralized vestibular loss, may include vertigo and nausea but is typically not associated with oscillopsia. With bilateral but asymmetric vestibular hypofunction, patients may present with a symptom profile that is consistent with both bilateral and unilateral vestibular loss, depending on the degree of asymmetry and the amount of loss in the better-functioning vestibular organ.

Vestibular Ototoxicity

Vestibular ototoxicity occurs when the damaging effects of a chemical substance are felt on the labyrinthine hair cells and their supporting structures, the vestibular division of the eighth cranial nerve, and its central nervous system connections.

The effects of this ototoxicity may be transient or permanent, and they can range from minimal to severe. The consequences for the person suffering from such a condition can be very debilitating.

Vestibular ototoxicity typically does not occur exclusively by itself but is often also accompanied by cochlear symptoms (hearing loss or tinnitus). Vestibular ototoxicity is said to be present when the symptoms of vestibular disturbances are more pronounced than those related to the cochlea [2, 3].

Diagnosing Ototoxicity

As previously noted, ototoxicity may present with symptoms related to the cochlea as well as the vestibular system. Evaluation of patients suspected of having ototoxicity requires a complete history and physical examination, including a comprehensive vestibular exam. Important elements of the vestibular exam to document vestibular hypofunction include head impulse testing in the planes of the three semicircular canals (see Halmgyi head impulse test below) and dynamic visual acuity testing.

Comprehensive testing includes electronystagmography (ENG) and videonystagmography testing with calories. Caloric testing, in particular, is used to document unilateral versus bilateral vestibular hypofunction.

Rotatory chair testing, if available, is also important in the diagnosis of vestibular hypofunction. Studies have shown that caloric and sinusoidal rotation tests are equally sensitive to monitoring the degree of nystagmus depression [4]. Some researchers have also demonstrated the distinct superiority of horizontal vestibular ocular reflex (VOR) rotational stimuli over caloric tests, especially when there is streptomycin-induced vestibular toxicity [5]. Another advantage of rotational testing is that high-frequency information unavailable from caloric testing can be obtained. Further, rotatory chair testing allows the clinician to track changes in the amplitude and symmetry of compensatory eye movements over a period of time. These can then be compared with normal values, which act as a referral, and the patient's progress can be monitored.

Dynamic posturography is an additional test that can be used. While it is generally insensitive to diagnosis, it is useful to document improvements in compensation over time. Further, it has made Romberg's test a sensitive one for evaluating the vestibular spinal reflex.

While the tests noted above are useful for the diagnosis and monitoring of vestibular compensation over time, in many instances, patients suffering from vestibular disturbances are quite ill and confined to bed. Thus, tests like complete ENG, rotation, and dynamic posturography cannot be easily performed on such patients. Longridge and Mallinson [6] described the "dynamic illegible E" for bedside evaluation of the VOR and VOR compensation. Its advantage is that it is simple to do, low cost, and can be performed at the bedside. Halmagyi and Curthoys [7] also describe a bedside test to determine the VOR. The examiner asks the patient to fix their gaze on the target while the examiner rapidly turns the patient's head from side to side. A normal patient does not make saccadic eye movements during the head rotation, indicating that the VOR is intact and that the patient's gaze has indeed been fixed. In contrast, patients with unilateral vestibular hypofunction can keep the gaze fixed on the target only when the head is tuned away from the abnormal side. When turning towards the side of the lesion, the patient must make one or more refixation saccades in the direction opposite to that of the motion of the head in order to allow his gaze to be fixed on the target. Patients with bilateral profound loss of vestibular function make saccadic refixation movements in both directions of passive head movements.

Audiometry

Aminoglycosides affect the outer hair cells of the basal turn of the cochlea. This usually results in high-frequency sensorineural hearing loss and a loss of speech understanding out of proportion to the loss of pure tone thresholds.

Electrocochleography has also been shown to be a very sensitive tool to determine hearing loss caused by ototoxic substances. It detects cochlear toxicity within minutes of an intravenous dose of intravenous aminoglycosides. Its disadvantage is that a needle has to be inserted through the tympanic membrane to make the measurement, limiting its widespread use.

Vestibulotoxicity Monitoring

No widely accepted guidelines exist for identifying vestibulotoxicity. The challenge of vestibulotoxicity monitoring as compared to cochlear ototoxicity is the identification of these symptoms. These become apparent only once the patients are mobilized.

Often, these symptoms are incorrectly attributed to the patient's debilitated state. There is no single test that can identify vestibulotoxicity. Screening tests, such as dynamic visual acuity and head impulse testing, can be used to monitor patients over time. Vestibular diagnostic procedures are often not feasible due to the patient's compromised health status.

Treatment

The treatment of vestibular ototoxicity can be divided into two parts.

1. *Vestibular ototoxicity* is expected when administering a medication that is potentially vestibular toxic. This can occur when administering aminoglycosides. Baseline audiometry and neurologic examination with specific attention to equilibrium are recorded and kept as a source of referral once treatment has been initiated. When patients are ambulatory, it is far easier to detect. Patients will report disequilibrium and other deficits almost immediately once they occur. Usually, these will be early and therefore easier to reverse. Reversal is usually accomplished with the cessation of the ototoxic medication.

   Those patients who are not ambulatory and are obtunded are less likely to report symptoms promptly. Thus, the severity will increase before the patient reports it. Usually, such patients will have other far more serious health problems, and the treating physician will likely have to choose between continuing or discontinuing the medication, especially if it is a life-saving drug.
2. *Protracted vestibular toxicity*. This is caused by frequent and prolonged use of ototoxic medication.

   These patients are the most difficult to treat. They will also present with other symptoms like tinnitus, decreased hearing, ataxia, and oscillopsia.

   While cochlear implants and other devices can ameliorate symptoms like hearing loss and tinnitus, disequilibrium remains the symptom that is most difficult to treat. Medications like Meclizine, which suppress vestibular responses,

generally are not much help in these circumstances after the acute phase of vertigo has resolved. Furthermore prolonged use of meclizine may result in other centrally mediated causes of imbalance and could complicate the treatment.

Benzodiazepines are not the treatment of choice. They are reported to adversely affect eye movements through reduction of saccadic velocity, increase in saccadic duration, impairment of slow pursuit, decrease in VOR gain, and increase in VOR time constant. They are also addictive.

Patients suffering from severe vestibular toxicity become visually and proprioceptor-dependent. They need visual cues to navigate and depend excessively on proprioception to walk. While they are able to see, walking is feasible. It is in the dark that such patients experience major difficulties.

Surgical options for this debilitating disorder are limited. Some have proposed either chemical (intratympanic gentamicin) or surgical labyrinthectomy to treat an ear that may be sending variable or abnormal balance signals to the brain, in the hopes that a better ear will allow improved vestibular compensation. However, such a procedure may in fact reduce the remaining vestibular function in a patient and make symptoms worse.

The question then arises: when both ears are affected, what treatment options exist? At present, the primary treatment used is vestibular therapy to help the patient compensate for the vestibular loss, both by utilizing any remaining vestibular function and by coordinating proprioception and vision into the patient's overall balance.

One future avenue of treatment that holds great promise is the vestibular implant [8]. It is similar to the cochlear implant in that it is a surgically inserted device in the vestibular end organs (at present limited to the semicircular canals) and restores VOR in these patients. The device is currently in clinical trials [9].

Overview

The diagnosis and effective treatment of ototoxicity are challenging. A stringent, practical protocol that encompasses all elements aimed at profiling the effects of ototoxicity is vital.

Ototoxic drugs usually adversely affect both the cochlea and the vestibular systems simultaneously. Currently, over 600 categories of drugs that have the potential to cause ototoxicity have been listed. Aminoglycoside antibiotics, platinum-based chemotherapeutic agents, loop diuretics, macrolide antibiotics, and antimalarials are the commonly used medications that have documented ototoxic effects. On questioning the patient, it has often been found that the exact time of commencement of symptomatology is frequently unclear. High interindividual variability in symptomatology is often found because of differences in genetic factors, pharmacokinetics, the metabolic status of the individual, and comorbid medical conditions.

Ototoxicity affecting the cochlea follows a relatively predictable pattern. The basal turn of the cochlea is involved first, involving its outer hair cells (responsible

for high frequencies), and as ototoxicity progresses, it involves the apical portion, which is responsible for the lower speech frequencies.

Although ototoxic-induced hearing loss is not a life-threatening condition, it can have a severely negative impact on communication and health-related quality of life issues, with significant adverse vocational, educational, and social consequences. It has been reported that in children, even mild hearing loss can severely impair speech and language acquisition and retard cognitive and social development. This, in turn, leads to poor scholastic performance and lowered psychosocial functioning. The goal of the management of ototoxicity is to minimize or prevent these complications and plan appropriate rehabilitation measures.

Preventive Measures

When administering a medication that is potentially ototoxic, especially if it is to be given as a course, it is prudent to get baseline measures of the cochlear and vestibular systems before starting treatment.

Baseline audiometric tests like pure tone, speech, and immittance audiometry need to be documented.

The question arises as to whether baseline vestibular testing should be carried out. If the patient is without vestibular symptoms, then perhaps rotatory chair testing can be performed. And findings were noted and documented. At this time, there are no clear protocols for pretreatment. Caloric testing can also be considered if the patient does not present with perforations or infections of the ear.

All aspects of treatment should and must be carefully explained to the patient in detail. The patient should be made aware of what the symptoms are that could herald the onset of either cochlear or vestibular toxicity.

Then should the patient present with symptoms, tests can be performed using the baseline as a comparison to determine the level of toxicity.

Some reports have described calcium as a competitive inhibitor of gentamycin. It was thought that an oral suspension of calcium could possibly be used as an oral supplement to avoid or ameliorate potential ototoxicity. It, in turn, could likely affect the efficacy of gentamycin. Thus, the pros and cons need to be carefully weighed before initiating it.

Still, some other researchers have described using probenecid to reduce the level of perilymph penetration of furosemide, resulting in diminished cochlear toxicity. Fosfomycin has also been reported as being able to reduce the effects of cisplatin ototoxicity.

There are several animal and in vitro studies that have reported the efficacy of otoprotective agents that can possibly prevent ototoxicity. Unfortunately, many of these studies lack appropriate control groups, positive clinical findings and longitudinal outcomes, and multicenter, large-scale clinical trials that would validate their results and recommendations. Agents designated as otoprotective medications such as sodium thiosulfate, amifostine, and *N*-acetylcysteine have been investigated for

cisplatin otoprotection. While systemic administration of these agents has been described as having the ability to reduce cisplatin-induced hearing loss, it was also found that they simultaneously reduce cisplatin's tumoricidal efficacy. Therefore, in an attempt to achieve otoprotection while simultaneously achieving tumoricidal activity, the administration of sodium thiosulfate was delayed for several hours following cisplatin administration. In addition, intra-tympanic administration of these agents was performed. There are reports of intratympanic administration of *N*-acetylcysteine, which adequately demonstrated otoprotection following the administration of cisplatin-induced ototoxicity. Intratympanic dexamethasone also yielded positive results following the administration of cisplatin.

Cisplatin-induced ototoxicity causes permanent hearing loss in pediatric and adult cancer survivors. Understanding the mechanisms that cause cisplatin-induced hearing loss and the development of treatment modalities to reduce and possibly reverse cisplatin ototoxicity have been impeded by animal models that are not ideal. In a clinical setting, cisplatin is frequently administered in multidose, multicycle protocols. However, many studies conducted on animal models used single injections of high-dose cisplatin. This does not reflect the manner in which cisplatin is administered in clinical protocols. When these rodents were subjected to similar protocols that occur in real-life clinical settings, there was significant mortality that again presented a major impediment to understanding the mechanisms of ototoxicity.

A Cochrane review of three randomized, controlled trials of amifostine agents reported that no conclusions could be drawn about their efficacy in otoprotection against cisplatin-induced ototoxicity in children. At this time, no medications have been approved by the US Food and Drug Administration that could play a role in the prevention of drug-induced ototoxicity during curative cancer treatment. More clinical research and trials are needed to study the otoprotective profile of these medications.

Recent studies have demonstrated the successful promotion of cochlear gene therapy, adeno-associated virus-mediated delivery of brain-derived neurotrophic factors, and stem cells in animal models. These future therapeutics hold promise for the prevention and treatment of ototoxicity, though much work needs to be done to document their efficacy and feasibility in humans.

Drug Metabolizing Genes and Its Association with Ototoxicity

Well-defined, clear associations have been established between chemotherapy and ototoxicity. Inter-individual variabilities have also been found in the development of chemotherapy-related hearing loss [10]. These interindividual variations can likely be explained by individual genetic variations toward the effects of chemotherapy, which in turn can potentially exacerbate the compound's ototoxic effects. Understanding these genetic variants as a way to predict which patients are most susceptible to ototoxicity could thus provide important information for clinical decision-making.

Candidate gene pharmacogenetic studies have explored the relationship between drug-induced hearing loss and several genotypes such as thiopurine methyltransferase, ATP-binding cassette transporter C3 (ABCC3), glutathione-*S*-transferase subclasses (GSTP1, GSTM1, and GSTT1), catechol-*O*-methyltransferase, and megalin [11–17].

These are results that are largely inconsistent. It was found that mutations in the mitochondrial DNA, such as the A1555G mutation, have been associated with increased susceptibility to aminoglycoside-related ototoxicity [18]. A recent genome-wide association study has identified the association between cisplatin-induced hearing loss and genetic variants such as superoxide dismutase 2 (SOD2) and Acylphosphatase-2 (ACYP2) ([19]).

Conclusions

1. Ototoxicity involves both the cochlea and the vestibular system.
2. There are no universally accepted, clearly defined protocols to evaluate and manage ototoxicity.
3. Most of the patients who are exposed to potentially ototoxic agents are obtunded and thus cannot complain of dizziness or hearing loss. When they do complain, ototoxicity is advanced, making treatment measures difficult.
4. There are a few medications available to ameliorate ototoxicity. However, they adversely affect the effectiveness of the medication that causes ototoxicity.

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