An overview of pharmacotherapy-induced ototoxicity

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Keywords: ototoxicity, pharmacotherapy, hearing loss, otoprotection, cochleotoxicity, vestibulotoxicity

Abstract

This article provides an overview of ototoxic medication, as well as different pharmacological and audiological monitoring strategies. Although ototoxic medications play an important role in modern medicine, they also have the capacity to do great harm and lead to significant morbidity. Physicians have to be aware of the potential effects of medication in order to identify patients who are at increased risk of developing ototoxicity. Precaution should be taken to prevent any auditory impairment that might occur through appropriate administration and monitoring. Although some otoprotective substances have been used successfully in certain studies, further trials must be performed to assess their clinical utility. The clinical pharmacist and audiologist form an important part of the ototoxicity management healthcare team.

Ⓟ **Peer reviewed. (Submitted: 2012-11-08. Accepted: 2013-02-18.)** **S Afr Fam Pract 2012;55(4):357-365**

Introduction

Ototoxicity is defined as damage to the inner ear after exposure to a toxic agent. These medications are used in patients where the use thereof is indicated to prolong life.[1] Other over-the-counter agents may also cause damage to the structures of the inner ear, but the hearing loss that results from these agents may not necessarily cause permanent damage.[1] Two specific drug classes have been identified to have the greatest potential to cause the highest degree of ototoxicity. These are the aminoglycosides and the antineoplastic drugs, especially cisplatin.[1]

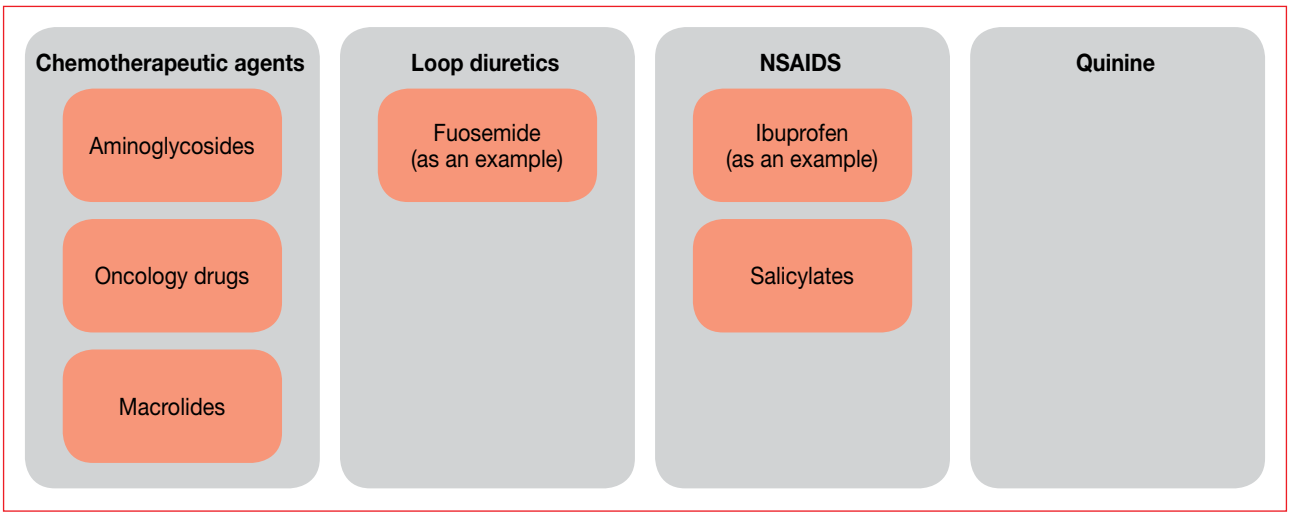
Ototoxic medications can either cause cochleotoxicity or vestibulotoxicity. Some medicines, like the aminoglycosides, can cause both. Cochleotoxicity may exhibit as hearing loss which may be permanent, tinnitus, and hyperacusis (increased sensitivity to everyday sounds), as well as difficulty with speech discrimination, especially in the presence of background noise.[2] Vestibulotoxicity may present as general disequilibrium, unsteadiness when walking or ataxic gait (a neurological sign associated with lack of voluntary coordinated muscle movement), oscillopsia (a subjective sensation that the environment is moving), nystagmus (involuntary abnormal eye movements) and/or vertigo.[2]

Implicated ototoxicity-causing drugs will be reviewed in this article (Figure 1).

Inner ear anatomy and physiology

The human cochlea is the portion of the inner ear that looks like a snail shell.[3] The cochlea is divided into three fluid-filled membranous channels, each of which is receptive to different sound frequencies. The middle channel is called the scala media and is filled with a potassium-rich fluid called endolymph. The basilar membrane serves as the base of this partition.[3] The organ of Corti is located on top of the basilar membrane and contains the sensory cells of hearing.[3] There are two types of sensory cells: outer hair cells and inner hair cells, both of which are unique and critical to the function of hearing.[3] These hairs cells are transducers and move with the basilar membrane.[3] Although both types of hair cells generate receptor potential, they perform different functions.[3] Inner hair cells are the sensory receptors that are responsible for more than 90% of the afferent information that is sent to the central nervous system.[4] Outer hair cells can contract. Therefore, they function as motor units which amplify the movement of the basilar membrane in response to a stimulus. Some of this added energy is transmitted back through the middle ear, where it can be recorded as an otoacoustic emission.[4] A clear perception of a sound (very good sensitivity and frequency selectivity) depends on anatomical integrity, as well as on the functioning of the cochlear amplifier, represented by the outer hair cells.[4] The amplified sounds are then detected by the inner hair cells and the messages are sent to the auditory nerve and the brain.[5] Outer hair cells are the first part of the inner ear to be affected by ototoxicity.

The inner ear also plays an important role in maintaining balance and contains specialised sensory receptors that are responsible for the perception of forces associated with head movement and gravity.[6] The peripheral vestibular system consists of three semicircular canals and two otolith organs



NSAIDS: nonsteroidal anti-inflammatories drugs

Figure 1: Implicated agents in ototoxicity

(the utricle and saccule) which are sensitive to different types of motion.[6] The semicircular canals are filled with perilymph, and the semicircular ducts with endolymph.[6] The sensory organ of rotation (crista ampullaris) is located within the semicircular canal duct.[6] The crista ampullaris is a cone-shaped structure, covered in receptor cells called "hair cells".[6] The vestibular hair cells can be classified as type I or type II.[6] Type I hair cells consist of more stereocilia than type II cells, and are more sensitive to damage due to ototoxicity.[6] Both impart information to the corresponding neurons of the vestibular nerve.[6]

Pathophysiology in ototoxicity

The sensory structures of the auditory and vestibular systems lie behind a blood-labyrinth barrier that is similar to that of the blood-brain barrier.[3] Theoretically, only ions, amino acids, sugars and other compounds essential to cellular function within the inner ear should be transported through it.[3] Any breakdown in the barrier, including ototoxins that can traverse the barrier, immediately induces loss of the endolymphatic potential, with consequent elevation of sensory thresholds.[3] Clinically, this presents as hearing loss.[3] The common mechanism of the various drugs that cause ototoxicity seems to be generation of toxic levels of reactive oxygen.[7] Many of the drugs that are ototoxic seem to be nephrotoxic as well. The ion and fluid composition is regulated in a similar way by both organs.[7] Initially, ototoxicity affects the sensory cells within the basal region of the cochlea where high-frequency sounds are processed. Therefore, changes in hearing are usually first detected in the highest audible frequencies.[3] The functional consequences of induced ototoxicity, which are much more severe in infants than in adults, are very important.[3,7] Various illustrated drugs will be discussed as subparagraphs in this section (Figure 1).

Aminoglycosides

Infectious disease is the most common cause of infant and child mortality worldwide.[8] Overlapping clinical presentations of bacterial infection result in an empirical combination of antibiotics to cover the most common pathogens.[8] Aminoglycosides are among the most frequently used antibiotics in neonatology and are usually given to patients in whom sepsis is suspected.[9]

Streptomycin was the first isolated aminoglycoside to treat Gram-negative and Gram-positive organisms.[7] Ototoxicity was first experienced with streptomycin in 1945, in patients suffering from tuberculosis.[7] The following aminoglycosides can be used for the treatment for bacterial infections: gentamicin, amikacin, kanamycin, tobramycin, netilmicin, spectinomycin, neomycin, streptomycin.[10,11]

The aminoglycosides are clinically used to treat aerobic Gram-negative bacterial sepsis and tuberculosis.[11] The mechanism of action of the aminoglycosides involves inhibition of the 30S ribosomal subunit of the bacterial ribosomes, inhibiting further protein synthesis.[11]

The toxicity of the aminoglycosides is linked to the total administered dose and dosing frequency. Once-daily doses have been associated with a reduction in ototoxicity, rather than twice-daily or more regular dosing intervals. However, genetic susceptibility also has an influence.[7,10,11]

Mechanism of ototoxicity

An overview of the implicated mechanisms that cause ototoxicity is illustrated in Figure 2.[11]

Susceptibility and genetic predisposition of patients to aminoglycosides

Mitochondrial involvement has been suggested in patients with an inherited maternal hypersensitivity to aminoglycosides.[7,11] Several mutations in the mitochondrial DNA are linked to increased susceptibility in aminoglycoside-induced toxicity.[10] Although the aminoglycosides preferentially target bacterial ribosomes, the inner ear and the kidneys are also damaged in a selected number of patients. This may be because of reduction and inhibition of mitochondrial protein synthesis.[10]

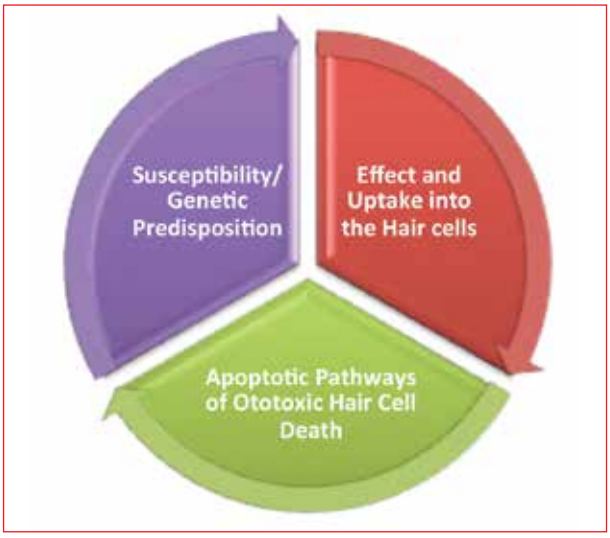


Figure 2: Mechanisms of ototoxicity induced by the aminoglycosides[11]

Genetic susceptibility has been illustrated to target the cochlea mostly, and not the vestibular organ or the kidneys.[10,11] This may be because of an increased affinity for mitochondrial rich tissues, and in these tissues it may cause misreading of the mitochondria, rather than direct inhibition of protein synthesis.[10,11] This may lead to a decrease in ion pump activity, resulting in a reduction in strial intermediate cells, as well as that in the endocochlear potential.[10] Ototoxicity can be induced after a single dose of the offending agent in patients who are genetically susceptible.[7,10,11]

Uptake into the hair cells

The aminoglycosides induce acute physiological and permanent functional effects.[7] The physiological effects include blockade of the ion channels. This may be mediated via endocytosis. Another mechanism might be due to the aminoglycosides blocking the depolarising transduction current of the mechanoelectrical tranducer (MET) channel.[7] The MET channel is located in the stereocilia, on top of the hair cells.[7] The rate of endocytosis is affected by temperature and is decreased by a reduction in temperature, such as in hypothermic conditions.[7] The MET channels can function like a one-way valve, promoting intracellular accumulation of the aminoglycosides. This may be aggravated by acoustic stimulation.[7] Noise and other acoustic stimulation enhances the "openness" of the MET channel, increasing aminoglycoside uptake.[7] This is especially true for patients who are treated in the noisy environment of the intensive care unit.[7]

Apoptotic pathways in ototoxic hair cell death

The uptake of the aminoglycosides leads to an increased formation of reactive oxygen species (ROS) or free radicals.[7,10,11] The cells normally protects themselves from ROS using intrinsic antioxidants, such as glutathione. These antioxidants can neutralise the ROS.[7,10,11] When a negative balance of ROS is obtained and overwhelms the capacity of the intrinsic antioxidants and repair systems, the cells undergoes apoptosis.[7,10,11] Intrinsic and extrinsic apoptotic pathways are also involved.[7,10] The extrinsic pathway ultimately leads to cellular degeneration mediated by death receptors, including the tumour necrosis factor. This activates caspases, leading to cellular degeneration.[7,10,11] The intrinsic pathway is the major pathway that is initiated by aminoglycosides that are triggered by non-receptor stimuli, like DNA damage, cytotoxic stress and cytokine deprivement.[7,10,11] Apoptotic death of the hair cells is better understood, but many parts of the cascade still needs to be investigated.[7,10,11]

Otoprotective strategies

The aminoglycosides are an important component of treatment regimens in South Africa, especially when treating tuberculosis. Various therapeutic strategies have been proposed to reduce the ototoxic effects of the aminoglycosides. Not all of the strategies have been fully tested, especially in the South African context. These strategies and selected examples are summarised in Figure 3.[2,7,10]

Oncology drugs

Platinum compounds

For the purposes of this paper, the main focus will be on the platinum compounds. Cisplatin is more ototoxic than carboplatin. However, carboplatin is also ototoxic, especially in certain sensitive populations, and when increased dosages are given.[12] Although cisplatin was used for its antineoplastic properties in the early 1970s, ototoxicity was only indentified in the 1980s.[13,14]

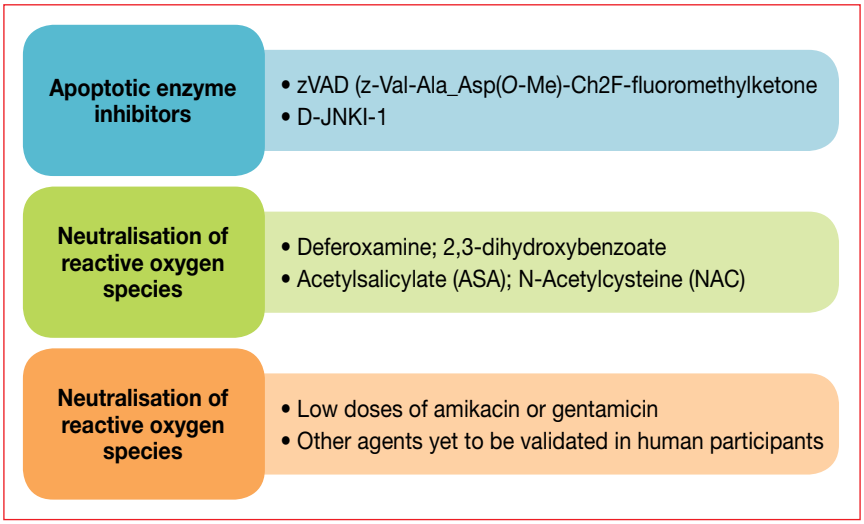


Figure 3: Otoprotective strategies[10]

When combined with other agents, cisplatin is used for the treatment of germ cell tumours in the testis, epithelial ovarian cancer, cervical cancer, squamous cell cancer of the head and neck, bladder cancer, lung cancer and lymphoma.[14]

Newer platinum compounds have been developed and are under development (second-, third- and fourth-generation compounds), and although currently it may seem that they have decreased ototoxicity, their clinical usefulness and post-exposure toxicity has not been fully established or proven.[14]

Mechanism of ototoxicity

The ototoxicity that is experienced by cisplatin is irreversible. Certain risk factors may increase the likelihood of ototoxicity developing[12-14] (Table I).

Table I: Risk factors for the predisposition of patients to ototoxicity[12-14]

Age extremes (very old and very young)
Previous history of hearing loss or auditory damage
Hydration status
Dose, duration and mode of administration
Renal insufficiency or insult
Use of other ototoxic agents
Cranial irradiation (current or previous)

Toxicity that relates to cisplatin is mostly cochlear, and causes high-frequency hearing loss due to damage to the outer hair cells in the organ of Corti.[14] Changes are also noted in the stria vascularis, spiral ganglion cells and the outer hair cells.[14] The depiction of hearing loss in these patients is illustrated in Figure 4, especially in patients who are treated with a total cumulative dose that is greater than 200 mg.[14]

Otoprotective strategies

The main focus is on strategies that reduce the formation of free radicals by temporal or anatomical separation of the platinum compounds with agents, including:[14]

- Vitamin E (α-tocopherol)
- Sodium thiosulfate
- D-methionine
- N-acetylcysteine.

Effectiveness in reducing ototoxicity, while still maintaining the anti-tumour effects, still needs to be fully illustrated and proven.[13,14]

Macrolides

Erythromycin was the first macrolide that was discovered in 1952. It obtained approval from the US Food and Drug Administration in 1964. Ototoxicity was first described in 1973.[15] Case studies on erythromycin with reversible and irreversible hearing loss have been described, and more recently with the newer macrolides: azithromycin, clarithromycin and roxithromcyin.[15-17]

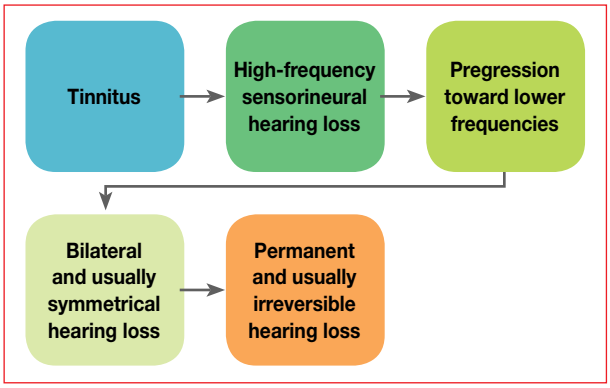


Figure 4: The presentation of ototoxicity (clinical) in patients who are treated with cisplatin[13,14]

The mechanism of action of the macrolides is inhibition of protein synthesis by reversible inhibition of the 50S ribosomal subunit.[18]

The clinical indications of the macrolides are summarised in Table II.[18]

Mechanism of ototoxicity

Risk factors that predispose patients to erythromycin ototoxicity include:[15]

- Renal impairment or a renal transplant.
- Hepatic dysfunction.
- Advanced age.
- Gender (females are at a higher risk).

The mechanism of ototoxicity for the macrolides is not fully understood, but following animal studies, ion transport impairment has been suggested at the level of the stria vascularis (peripherally), as well as central involvement in the auditory pathways.[15,16]

Loop diuretics

These diuretics comprise a group of diuretics that exert a diuretic effect by blocking the sodium and chloride from the epithelial cells in the loop of Henle and the proximal renal tubules.[19,20]

These drugs are also referred to as high-ceiling diuretics and are very useful in high doses to promote diuresis in patients with severe impairment of renal function.[18] Drugs that are used in this class include furosemide, torasemide and bumetanide.[18,19]

Their clinical application includes the oedema of cardiac, hepatic or renal origin, mild to moderate hypertension in patients with renal impairment, oliguria due to intrinsic renal failure, and patients suffering from hypercalcaemia.[18,19]

Mechanism of ototoxicity

Sensory hearing loss as a result of the loop diuretics may be transient or permanent.[19,20] Hearing loss may present as sensorineural hearing loss with vertigo, indicating that vestibular toxicity may also be present.[19,20]

Table II: Clinical applications of the macrolides[18]

Erythromcyin	Azithromycin	Clarithromycin	Roxithromycin
Used as a penicillin alternative in patients who are allergic to penicillin.	Has a similar spectrum and clinical application to that of erythromycin, with a longer half-life and less gastrointestinal side-effects.	Has a similar spectrum and clinical application to that of erythromycin, with a longer half-life and less gastrointestinal side-effects.	Has a similar spectrum and clinical application to that of erythromycin, with a longer half-life and less gastrointestinal side-effects.
Used for various infections caused by atypical organisms.	Also useful for treating chlamydial infections when doses are given at 1g.	Used with a proton-pump inhibitor in the treatment and eradication of *Helicobacter pylori*.	
	Used for rickettsial infections.	Used for *Mycobacterium avium* infections, in combination with ethambutol.	

Various mechanisms are involved in ototoxicity (Figure 5).[19,20]

Patients with the following conditions are at greater risk of loop diuretic-induced ototoxicity:[19,20]

- Renal impairment
- Premature infants
- Concomitant use of aminoglycoside antibiotics.

Hypoalbuminemia have been postulated to play a role in the ototoxicity induced by furosemide as it is 98% protein-bound.[19]Any clinical conditions which cause hypoalbuminemia will also bring about an increase in the free fraction of available furosemide.[19] The increased amount of available furosemide predisposes the patient to increased risk of ototoxicity.[19]

Compared to furosemide, bumetanide seems to be more potent and less ototoxic and can be used as an alternative in patients suffering from furosemide-induced ototoxicity.[20]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally used in everyday practice as painkillers for musculoskeletal and inflammatory conditions.[18] Drugs in this category include ibuprofen, diclofenac, indomethacin, aspirin (at therapeutic dosages) and mefenamic acid.[18]

Their actions stem from their ability to inhibit prostaglandin production by inhibiting cyclo-oxygenase (COX).[21,22] Through COX inhibition, prostaglandin biosynthesis is also inhibited. There are two forms of COX: cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-II (COX-2).[21] COX-1 has spliced variants. One of the these has been called COX-3.[21,22]

COX-1, but not COX-2, is expressed in the gastric epithelial cells and is the major source of cytoprotective prostaglandin formation.[21] Thus, when the nonselective NSAIDs inhibit COX-1 and COX-2, the patients experience gastric side-effects (although in recent literature, the selectiveness of the side-effects with the newer-generation selective COX-2 inhibitors has been questioned).[21,22]

Mechanism of ototoxicity

The severity of the ototoxicity experienced with the NSAIDs correlates with the level of the salicylate.[21] High-dose

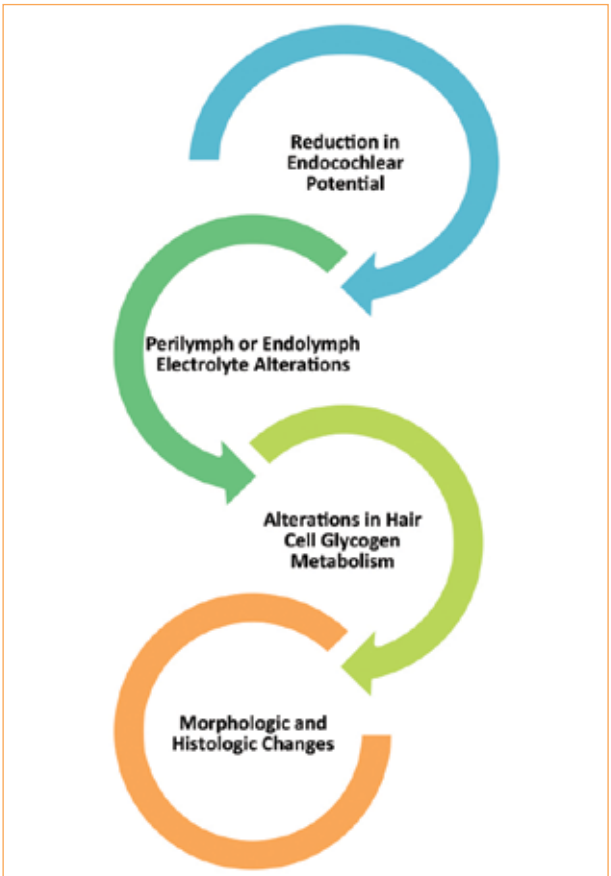


Figure 5: Mechanisms involved in ototoxicity that is induced by the loop diuretics[19,20]

NSAIDs inhibit cochlear movement. The NSAID ototoxicity reflects OAE, with repeated reduction of the OAE level.[21,22]

The NSAIDs cause the following:[21,22]

- Mild to moderate sensorineural hearing loss with impaired sound amplification of the outer hair cells due to direct action on the motility.
- Degeneration of the spiral ganglion neurons at high dosages, with impaired auditory neural activity of the cochlea.
- The arachidonic acid augments N-methyl-D-aspartate receptor currents. These receptors are expressed by the spiral ganglion neurons. Stimulating these receptors causes patients to experience tinnitus.

- Central activity includes abnormal excitability of neurons in the brainstem, subcortical area and auditory cortex.
- Reduction of blood flow to the cochlea, with possible vasoconstriction of the capillaries of the spiral ligament and stria vascularis.

The ototoxicity is reversible and transient and may cease after the NSAIDs have been stopped.[21] The NSAIDs also have protective effects. This will be discussed in the next section.[21]

Protective mechanisms of the nonsterioidal anti-inflammatory drugs when used for cochlear injury

The protective effects of the NSAIDs when used for inner ear injury are not fully understood, but might be attributable to their anti-inflammatory and antioxidant actions.[21,22]

Other postulated mechanisms include:[21,22]

- *Antioxidant properties:* The ROS is responsible for several inner ear injuries as a result of medicine, loud sounds, ischaemia and ageing.
- *Regulation of the transcriptional factor nuclear factor kappa B (NF-χB):* This inhibits the apoptotic pathway.

Further investigations are needed to clarify the protective effects.

Quinine

Quinine's manifestation of ototoxicity and the salicylates is very similar, but the mechanism of toxicity is very different.[22] In the era of chloroquine resistance, quinine is used to treat malaria, specifically *Plasmodium falciparum,* or if the *Plasmodium* spp. is unknown.[18,22]

It is also used as a muscle relaxant in the treatment and management of myotonic contractions and nocturnal leg cramps. This practice is not recommended because of quinine's toxicity.[18]

Mechanism of ototoxicity

A large dose of quinine leads to reversible hearing loss and tinnitus, with cochlear outer hair cell involvement.

It has been proposed that the following actions cause ototoxicity:[22]

- Hyperpolarisation, followed by depolarisation of the hair cell membrane potential, with dose-dependent responses that are reversible.
- Reduction in the cochlear blood flow, with possible vasoconstriction. Reduction in blood flow has been noted in the capillaries of the basilar membrane.
- By binding to plasma proteins, quinine triggers the complement cascade. This may lead to disseminated intravascular coagulation, thrombocytopenic purpura and haemolytic anaemia in susceptible individuals. This can be attributed to the microvascular changes in the cochlea.

The hearing loss that is experienced with quinine is mostly reversible. However, permanent hearing loss that interferes with conversational frequencies has been reported.[22]

The ototoxicity that is experienced with quinine manifests as hearing loss (mostly transient), tinnitus and vertigo, with associated vestibular toxicity.[22]

Beverages that contain small amounts of quinine may lead to low-serum quinine levels which can be significant enough to cause positional changes.[22] The amount that is needed for this is 1.6 l of tonic water (105 mg) daily for two weeks.[22]

Audiological monitoring of ototoxicity

The effectiveness of particular test protocols in detecting and monitoring ototoxicity depends on a variety of factors, such as the status or responsiveness of the patients, the speed of the tests, the costs that relate to performing the different tests, as well as the availability of equipment.[23] Proper objective and subjective monitoring of cochlear and vestibular function may help with recognition of the toxic effect of the medication.[23] Early identification and monitoring of ototoxic damage provides opportunities to counsel the patient and/or his or her family, by providing information on symptoms, side-effects and specific management strategies.[23]

Cochleotoxicity monitoring

Patients who are treated with ototoxic drugs may experience hearing loss that can negatively impact on the communication process, coping skills and quality of life.[24] Early detection of ototoxicity must include direct auditory function assessment.[24] Audiological tests must be sensitive to ototoxic damage and must be specific and reliable across measurements.[24] Significant clinical change is described in terms of documented normal variability between baseline and follow-up assessments.[24] Early identification of ototoxic hearing loss is critical to facilitating alternative treatment, wherever possible, that can minimise or prevent communication impairment.[24] Over the past decade, three main approaches to aetiological monitoring of ototoxicity have emerged[24] (Figure 6).

Although the basic audiological assessment may not detect early ototoxic changes, it evaluates the patient's hearing in the speech frequency range for communication, calculates word recognition ability and middle-ear functioning via tympanometry, and detects whether there is co-existing pathology.[25] The foundation of ototoxicity monitoring is the serial collection of ultra-high frequency audiometry and/or evoked otoacoustic emission testing.[25] These two techniques can identify ototoxic damage earlier than conventional pure-tone threshold testing.[25] Tinnitus assessment methods, as well as auditory brainstem response (ABR) testing, can form part of the assessment and monitoring protocol.[25]

Audiological monitoring for ototoxicity consists of objective measures in neonates and other unresponsive patients.[3] This consists of electroacoustical and electrophysiological procedures that serve both as indices of hearing sensitivity, and as indications of the site of lesion in the auditory

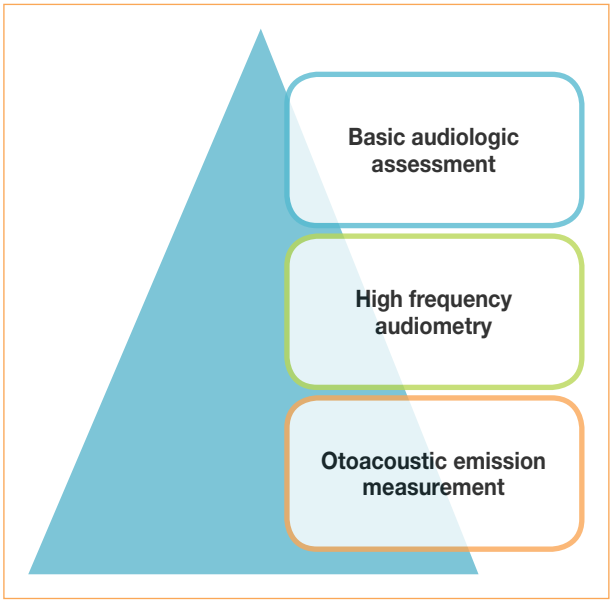


Figure 6: Approaches to the aetiological monitoring of ototoxicity[24]

system. These tests do not require behavioural responses from patients.[3] It is important to obtain a baseline reading of audiological tests for every individual, preferably prior to any treatment to allow future comparisons to be made.[3]

Otoacoustic emissions

OAEs provide an objective evaluation of the cochlear outer hair cell system and are considered to be a sensitive test for detecting and monitoring even small changes in the inner ear due to ototoxicity.[4] OAEs are measurable echoes emitted by the normal cochlea which relate to the function of the outer hair cells.[4] A sensitive microphone placed into the ear canal is used to monitor the existence of the response following stimulation.[3] The outer hair cells are among the first inner ear structures that are damaged by aminoglycosides. Early changes in OAEs may reflect subclinical cochlear damage that could progress to a clinically relevant hearing loss if treatment is continued.[23]

The two types of applied clinically OAE are the transient-evoked OAE and the distortion-product OAE.[23] The most common stimuli for transient-evoked OAEs are clicks, although transient-evoked OAEs can also be recorded with tone burst stimuli.[23] Click stimulation includes a broad band of frequencies and activates the cochlea simultaneously with the basal to apical regions of the basilar membrane.[23] Distortion-product OAEs are elicited by the simultaneous presentation of two pure tones, closely spaced in frequency. The distortion-product OAE response is the actual intermodulation distortion-product that is produced by the ear when it is stimulated by these two tones.[4] An implicit issue is whether the transient-evoked OAEs and distortion-product OAEs are equally efficacious in detecting ototoxic changes. Testing distortion-product OAEs may detect ototoxic change earlier than transient-evoked OAEs.[26] Practically, distortion-product OAEs can be measured at higher frequencies than transient-evoked OAEs, thus being more sensitive to the cochlear frequency areas that are first affected.[26] The distortion-product OAEs can often be recorded in the presence of more severe sensorineural hearing loss than transient-evoked OAEs, rendering more patients eligible for OAE monitoring.[27]

Lastly, with ototoxicity, OAEs have been shown to decrease simultaneously with changes in high-frequency audiometry thresholds and before changes appear in the conventional audiometric frequencies.[25] This is important as commercially available OAE systems tend to have insufficient output for stimuli above 8 kHz and increased system distortion at the higher frequencies.[25] Standard calibration procedures for inserted earphones that are used in OAE applications can produce errors at high frequencies which depend on probe insertion depth and fit, adding variability for repeated OAE measures. This can negatively influence the monitoring process.[25] Changes in outer hair cell function are seen as decreases in distortion-product otoacoustic emission amplitudes, decreases in the dynamic range of the response (signal to noise ratio), and/or loss of distortion-product otoacoustic emission specific to regions of outer hair cell damage.[4] The accepted criteria for ototoxicity detection using OAEs ranges between 2.4 and 7 dB sound pressure level at 1-4 kHz.[28]

Automated auditory brainstem response

Automated ABR is an auditory-evoked potential, originating from cranial nerve VIIII and auditory brainstem structures in response to a sound stimuli presented to the ear.[3] The ABR wave forms consists of 5-7 peaks that reflect stimulus-evoked electrical signals along the auditory pathways from the auditory nerve to the inferior colliculus of the brainstem, representing neural function of the auditory nerve.[3] The ABR is recorded using scalp electrodes and is best induced by an auditory stimulus that has a rapid onset, e.g. a click or tone burst.[3] The ABR is recorded using scalp electrodes and is best induced by an auditory stimulus that has a rapid onset, e.g. a click or tone burst.[3] The ABR can register changes in amplitude and/or latency of neural responses as a result of ototoxicity.[23] ABRs are reliable, somewhat portable and noninvasive. Responses can be recorded in ears with more severe pre-existing hearing loss, when compared with the limits of OAEs.[3]

Ultra-high-frequency tone burst stimuli (8-14 kHz) have been used in ABR testing and has good test-retest reliability, a requirement for serial monitoring of ototoxicity, and generally correlates well with behavioural thresholds.[29] As with OAEs, variability in the relationship between ABR measures and audiometric thresholds matters less than the ability of the objective measure to monitor changes over time.[29] Despite its effectiveness, the ABR test is lengthy and lacks frequency specificity at very high stimulus levels.[29] In addition, output is limited when high frequencies are used, largely because of transducer constraints. Response interpretation can be variable and subjective.[29] Tone bursts in multiple sequences allow more stimuli to be presented in a shorter time period and to have good reliability.[30]

Table III: Comparison of audiological ototoxic monitoring techniques[3,4,23,25]

	Basic audiometry	High-frequency audiometry	Otoacoustic emissions	Automated auditory brainstem response
Advantages	Assesses hearing in the speech-frequency range.	Is the most sensitive test for early ototoxic damage to the inner ear.	Is an objective test of the cochlear outer hair cell system.	Is an objective test procedure.
	Identifies co-existing pathology that can affect test results (differential diagnosis).	Criteria of change that relates to ototoxicity is established. Therefore, it is valuable in identifying and monitoring ototoxicity.	Is sensitive to early ototoxic changes.	Has good test-retest reliability.
			Is time-efficient.	Is noninvasive.
			Is the test of choice in the paediatric population.	Can be used in cases of moderate hearing losses.
Disadvantages	Is less sensitive in detecting early ototoxic changes.	Is not standardised.	Results depend on probe-insertion depth and fit (variability).	Is lengthy.
	Has a limited frequency test range.	Is problematic in patients with hearing loss.	Is affected by middle-ear pathology.	Has output restraint for the high frequencies.
			Criteria for change indicating ototoxicity is proposed in the literature, but there is no universal value.	
			Is problematic in patients with hearing loss.	

Table IV: Quantitative techniques for vestibular function[31]

Quantitative techniques for vestibular function	Informal (bedside) quantitative techniques for vestibular function
Dynamic visual acuity test Impulse testing, e.g. vHIT Videonystamography Posturography Rotation chair Vestibular-evoked myogenic potential	Head thrust test Head shake nystagmus Postural control Head impulse test

vHIT: video head impulse test

A summary of the advantages and disadvantages of the different cochleotoxicity monitoring techniques is provided in Table III.

Vestibulotoxicity monitoring

Vestibular toxicity can vary from a minimal, clinically undetectable disturbance to a total bilateral loss of vestibular function.[31] The degree mostly depends on the extent of cellular damage within the vestibular end-organ.[31]

The clinical features that make the monitoring of vestibular function for ototoxicity a challenge include:[31]

- Delayed onset from the beginning of treatment.
- Possible spontaneous reversibility of vestibular symptoms.
- A striking difference in the clinical presentation of unilateral and bilateral vestibular loss in patients.[31]

No widely accepted guidelines for vestibulotoxicity monitoring exist.[31] A number of possible quantitative techniques may be used to assess vestibular system function (Table IV).[31] Informal or "bedside" tests may also be used to identify bilateral peripheral vestibular system impairment (Table IV).[31]

However, these information tests are sensitive to impairments of high-frequency function and are not helpful in identifying the earliest signs of bilateral peripheral vestibular system impairment.[31] Finally, self-report measures of dizziness disability include the Dizziness Handicap Inventory, which is a simple paper questionnaire.[32] Early recognition of signs and symptoms of vestibulotoxicity is important as the window for recovery is often short.[32]

Managing ototoxicity

The management of cochlear toxicity entails appropriate schedules of therapy, the association of presumed protectors, monitoring and referral for hearing aids, cochlear implants and/or assistive technology.[32] The process starts with the prevention or minimisation of permanent impairment by selecting less ototoxic drugs and by identifying high-risk patients.[32] Early identification and counselling includes the provision of information and support to the patient and/or the family in order to make informed decisions.[23] Vestibular rehabilitation therapy (VRT) is considered to be effective in treating vestibulotoxicity.[32] VRT is an exercise-based treatment programme designed to promote vestibular adaptation and substitution by

facilitating vestibular recovery mechanisms. These mechanisms include vestibular adaptation, substitution by the other eye-movement systems, substitution by vision, somatosensory cues and other postural strategies. VRT is indicated for any stable, but poorly compensated vestibular lesion, regardless of the patient's age, the cause, symptom duration and intensity.[32]

Interdisciplinary communication

A coordinated and cooperative effort should be maintained by the patient or caregiver's primary physician; the ear, nose and throat (ENT) specialist; audiologist and clinical pharmacist in order to detect cochleotoxicity as soon as possible.[23] It is particularly essential that the ENT and the audiologist are made aware of the name of the drug, the dosage, any changes in the medication regimen, the manner of the drug's absorption and excretion, the status of the patient's kidney and liver functions and the patient's risk factors for ototoxicity.[23] Conversely, the audiologist should relay the otological status to the patient or caregivers at the time of testing.[23] The audiologist might be the first member of the management team to recognise subtle changes in the patient's cochlear function. This information should be relayed to the healthcare team to ensure optimal management.[23]

Conclusion

Various drugs can result in hearing loss, which may or may not be reversible. Certain mechanisms are responsible for the hearing loss, which can either be cochleo- or vestibulotoxic. Unfortunately, hearing loss induced by pharmacotherapy may go unnoticed until a communication problem becomes apparent, signifying that hearing loss has already occurred within the frequency range that is important for speech understanding. Similarly, by the time a balance problem is noticed in patients, permanent vestibular system damage has probably already occurred. Cochlear and vestibular deficits can also result in social, emotional and vocational problems. Therefore, early detection of ototoxic-induced hearing loss is essential for patients. Ototoxic monitoring provides an opportunity for the consideration of alternative treatment regimens to minimise or prevent hearing loss progression. Both the clinical pharmacist and the audiologist play a critical role in the process of ototoxic monitoring. They function as advisers to the physician within the healthcare team by providing reliable data, while educating and counselling the patient.

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