

Clinical pharmacology

Drug-induced ototoxicity

Sensorineural hearing loss, the commonest type of hearing loss, is defined as hearing loss originating from damage to the vestibulocochlear nerve, inner ear or the brain. Hearing loss affects 30% of the international community. In South Africa, the estimated prevalence of infants with hearing loss is 5.5/1 000 live births. Hearing loss can be inherited or acquired. Hereditary hearing loss may be syndromic (e.g. Down's syndrome) or non-syndromic. Although the causes for acquired hearing loss have not been systematically evaluated, generally, major causes of childhood hearing loss include infections such as meningitis, measles, otitis media and different febrile illnesses, which are often undertreated. In addition to disease complications, acquired hearing loss may be caused by exposure to noise, environmental toxins (radiation, organophosphates) and ototoxic drugs (Table I).

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A drug is considered ototoxic if it has the potential to cause toxic reactions to structures of the inner ear, including the cochlea, vestibule, semicircular canals and otoliths, thus causing sensorineural hearing loss.

Drug damage to the auditory and vestibular structures may cause hearing loss, tinnitus, disequilibrium or dizziness. The hearing loss may be transient, progressive or permanent. Aminoglycosides, platinum-based chemotherapeutic agents and quinine (especially in high malaria areas) cause permanent hearing loss. Loop diuretics, e.g. furosemide, salicylates and phosphodiesterase type 5 inhibitors, e.g. sildenafil, can cause transient hearing loss. The severity may range from slight to profound, and is usually bilateral and symmetrical. Time to onset is often

Table I. Examples of drugs known or reported to be ototoxic

Ototoxic drug class	Examples
Aminoglycosides	Streptomycin, amikacin, tobramycin, gentamycin, kanamycin, capreomycin
Platinum-based chemotherapy	Cisplatin, carboplatin, oxaliplatin
Loop diuretics	Furosemide, torasemide, bumetanide, piratenide
Other antibiotics	Erythromycin, vancomycin
Antimalarials	Quinine
Salicylates	Aspirin
Phosphodiesterase type 5 inhibitors	Sildenafil, tadalafil, vardenafil

unpredictable, and marked hearing loss is known to occur even after a single dose. However, hearing loss may not manifest until several weeks or months after completion of a course of an ototoxic drug.

Pathophysiology of ototoxicity

The mechanism of aminoglycoside ototoxicity is mediated by disruption of mitochondrial protein synthesis and the formation of free oxygen radicals. The cellular basis for aminoglycoside hearing loss is a destruction of cochlear hair cells, specifically the outer hair cells. Aminoglycosides generate free radicals within the inner ear by activating inducible nitric oxide synthetase and therefore increasing nitric oxide concentrations. Oxygen radicals then react with the nitric oxide to form the destructive peroxy nitrite radical, which can directly stimulate mitochondrial-mediated apoptotic cell death. This leads to permanent damage to the outer hair cells of the cochlea, resulting in permanent hearing loss. There is synergistic toxicity with noise exposure. The synergistic toxicity of noise exposure and aminoglycoside antibiotics is not limited to simultaneous exposures. Prior acoustic insult, which does not result in permanent threshold shifts, potentiates aminoglycoside ototoxicity. In addition, exposure to sub-damaging doses of aminoglycosides aggravates noise-induced cochlear damage. The presence of specific mitochondrial DNA mutations (e.g. A1555G) also increases the risk of aminoglycoside-induced ototoxicity.

The mechanism of platinum ototoxicity is mediated by free-radical production and cell death. Platinum compounds damage the stria vascularis (columnar epithelium with capillaries which secretes endolymph

in the scala media) and cause outer hair cell death beginning at the basal turn of the cochlea. Free-radical species are produced by NADPH oxidase in the inner hair cells following cisplatin exposure. NADPH oxidase is the enzyme that catalyses the formation of superoxide radicals. NOX3 is a particular form of NADPH oxidase that is highly and selectively produced in the inner ear and is an important source of free-radical generation in the cochlea, which might contribute to hearing loss. The free radicals generated by this mechanism then lead to mitochondria-mediated and caspase (protease)-mediated apoptotic cell death, and ultimately permanent hearing loss.

The ototoxic effects of loop diuretics seem to be associated with the stria vascularis, which is affected by changes in the ionic gradients between the perilymph and endolymph. Oedema of the epithelium of the stria vascularis results from these ionic changes. Hearing loss is usually dose dependent and follows intravenous bolus injections. It is usually self-limiting, but irreversible hearing loss has been reported, especially in neonates.

Salicylic acid rapidly enters the cochlea, and perilymph levels correspond to serum levels. Rising levels produce tinnitus and, generally, a reversible flat sensorineural hearing loss. The mechanism is multifactorial but appears to cause metabolic rather than morphological changes within the cochlea.

A few case reports have documented an association between phosphodiesterase type 5 inhibitors and transient hearing loss. The mechanism is thought to be related to their effect on the nasal erectile tissue with subsequent blockade of the eustachian tube, related to the peak plasma levels.

Mitochondrial toxicity associated with use of nucleoside reverse transcriptase inhibitors (NRTIs) has also been implicated in older HIV-infected patients who develop hearing loss.

As the most commonly used ototoxic drugs cause irreversible hearing loss, and there is no medical treatment to date, early detection and intervention is of critical importance.

Who is at risk for ototoxicity?

Risk factors for ototoxicity include extremes of age (e.g. degenerative hearing loss), renal impairment, strong family history of hearing loss (e.g. genetic predisposition to aminoglycoside-induced ototoxicity due to mitochondrial DNA mutations), exposure to noise, cranial irradiation and ototoxic agents.

Ototoxicity risk increases with higher doses of ototoxic agents, elevated serum

levels and prolonged (e.g. cumulative aminoglycoside exposure in the management of multidrug-resistant tuberculosis) or repeated exposure (e.g. repeated cycles of platinum-based chemotherapy) to these agents.

Prevention of ototoxicity

As the most commonly used ototoxic drugs cause **irreversible** hearing loss, and there is no medical treatment to date, early detection and intervention is of critical importance. If there is an alternative agent, ototoxic drugs should be avoided. Noise exposure should be minimised.

Persons at risk, e.g. neonates with previous exposure to aminoglycosides, should have their hearing tested, as optimal developmental outcomes are achievable if intervention is undertaken between 6 and 9 months of age.

In a nutshell

- Drug-induced ototoxicity may have serious communication, educational, and social consequences.
- Prevention is the mainstay, as most agents cause irreversible damage, followed by screening and serial monitoring in patients at risk for early detection and intervention.

- Simultaneous noise exposure or concomitant use of ototoxic drugs should be avoided.
- Risk benefit assessment must occur and, where appropriate, alternative less ototoxic medications considered.

Further reading

Bardien S, de Jong G, Schaaf HS, Harris T, Fagan J, Petersen L. Aminoglycoside-induced hearing loss: South Africans at risk. *S Afr Med J* 2009; 99: 440-441.

Gibbon CJ, Blockman M, eds. *South African Medicines Formulary*, 8th ed. Cape Town: Health and Medical Publishing Group of the South African Medical Association, 2008.

Okuyucu S, Guven OE, Akoglu E, Uçar E, Dagli S. Effect of phosphodiesterase-5 inhibitor on hearing. *J Laryngol Otol* 2009; 123: 718-722.

Simdon J, Watters D, Bartlett S, Connick E. Ototoxicity associated with the use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. *Clin Infect Dis* 2001; 32: 1623-1627.

Swanepoel D, Störberg C, Friedland P. Early hearing detection and intervention in South Africa. *Int J Pediatr Otorhinolaryngol* 2009; 73: 783-786.

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