Ototoxicity

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Ototoxicity can be defined as the tendency of certain substances, either systemic or topical, to cause functional impairment and cellular damage to the tissues of the inner ear and especially to the end organs of the cochlear and vestibular divisions of the eighth cranial nerve[1].

Major systemic ototoxic substances include;

- Aminoglycosides
- Salicylates and nonsteroidal anti-inflammatory drugs
- Loop Diuretics
- Platinum Compounds
- Iron chelating agents
- Macrolides

Major topical ototoxic substances include;

- Topical Aminoglycosides
- Topical Chloramphenicol
- Topical Polymyxin
- Topical Antifungals
- Surgical Disinfectants and Antiseptics

Aminoglycosides Ototoxicity

Aminoglycoside antibiotics are effective against aerobic gram negative (-ve) bacilli and also have some effect against Staph aureus. Their use however has been in decline since the introduction of broader spectrum antibiotics specifically the floroquinolones and because of concern regarding their toxicity. Their major toxicities are nephrotoxicity, ototoxicity and neuromuscular blockade (that can occur during general anesthesia). Aminoglycosides in common use include; gentamicin, amikacin, kanamycin, neomycin, netilmicin, paromycin, streptomycin, spectinomycin and tobramycin. From these drugs only gentamicin, neomycin and tobramycin are available in topical preparations. Aminoglycosides are used in various illnesses:

- Septicemia
- Serious urinary tract infections
- Osteomyelitis
- Intra-abdominal infections
- Serious respiratory tract infections
- Serious infections with pseudomonas species
- Enterococcal endocarditis
- Listeria monocytogenes
- Mycobacterial infections(streptomycin is often recommended)
- Non-tuberculous mycobacterial infections(amikacin is often recommended)

Nephrotoxicity results from acute tubular necrosis as all aminoglycosides appear to concentrate in the renal tubular cells. The incidence of nephrotoxicity has been estimated at about 15%[1].

Ototoxicity results from hair cell destruction in the cochlea and vestibule. The incidence varies in the literature but on average is about 5% [1]. Ototoxicity can occur both from systemic and topically administered drugs. Although this is less common than nephrotoxicity the damage is usually permanent and not reversible.

Risk factors for aminoglycoside ototoxicity include;

- Genetic susceptibility (related to two mutations on the mitochondrial DNA mainly seen in Chinese and Japanese families to date)
- Prolonged duration of therapy
- Bacteremia
- Renal dysfunction
- Fever
- Liver failure
- Advanced age
- Co-administration of ototoxic drugs
- High serum concentration
- Preexisting hearing loss

Neomycin seems to be the most toxic overall followed by kanamycin, gentamicin, tobramycin, amikacin and netilmicin in that order.

Safe Administration requires full risk-benefit assessment. Once daily dosing should be used whenever possible to minimize nephrotoxicity and serum concentrations should be monitored. Renal function should be checked regularly. Base line hearing and balance testing should be performed especially when prolonged treatment is anticipated.

Salicylates and Nonsteroidal Anti-inflammatory Drugs & Quinine

Salicylates and nonsteroidal anti-inflammatory drugs (NSAID) are in wide use. They are also available over the counter.

The ototoxicity of salicylates seems to be mainly reversible with recovery occurring within 24 to 72 hours after stopping the drug. They may cause tinnitus and sensorineural hearing loss (SNHL) at high doses[2].

The mechanism for salicylate ototoxicity has been detected in the ultrastructural level by electron microscopy. There are morphologic changes in the outer hair cells (OHC's) [3]. Most animal studies show an increase in spontaneous activity of auditory neurons after salicylate administration. Various reports have shown reduction of spontaneous otoacoustic emissions (OAE's) which further suggests an OHC abnormality. Another mechanism has been reported to be a reduction in cochlear blood flow[3].
The otoxicity of the NSAID are thought to be similar to salicylates.

Quinine is used as a treatment of malaria and muscle cramps. Its use has also been associated with hearing loss and tinnitus. Although hearing loss is reversible a permanent loss occasionally occurs as well.

The mechanism for quinine ototoxicity is not very clear but seems to be similar to salicylates for the most part.

Heavy Metals such as mercury (Hg) and lead (Pb) are ototoxic. Sub-clinical mercury toxicity can be detected by Auditory Brainstem Recordings (ABR) showing prolongations of wave I-V. Lead has a toxic effect on both the peripheral and central nervous system and therefore can affect the entire auditory pathway.

Loop Diuretics

Furosemide, bumetanide and ethacrynic acid are the most commonly used loop diuretics.

Ethacrynic acid is a loop diuretic that has been identified to cause SNHL, tinnitus and vertigo.

Mechanism for its ototoxicity may be due to;

1. a reduction in endocochlear potential
2. electrolyte alteration in perilymph and endolymph
3. alteration in hair cell glycogen metabolism
4. morphologic changes in stria vascularis[4]

Furosemide is the most widely used loop diuretic. Most cases of furosemide ototoxicity seem reversible4.

Risk factors for ototoxicity include;

- Renal failure
- Use in premature infants
- Hypoalbuminemia
- Intravenous rapid bolus dose
- Co-administration of aminoglycoside

Mechanisms for furosemide ototoxicity include;

- Reduction of endocochlear potential and auditory electrical potentials
- Morphologic and histologic changes in the endolymph/perilymph barrier, strial vascularis, endolymphatic sac and changes in the OHCs.
- Biochemical changes

Bumetanide is a very potent diuretic and seems less ototoxic than furosemide.

Platinum Compounds

These compounds are used as chemotherapeutic agents and include cisplatin, carboplatin, nedaplatin and oxaliplatin.

Cisplatin is widely used in gynecologic, testicular, lung, central nervous system and head and neck cancers. It generally causes a high frequency SNHL initially which can worsen with continued therapy.

Risk factors for ototoxicity include;

- Age extremes
- Renal failure
- High dosage
- Co-administration with aminoglycosides or loop diuretics
- Excessive noise exposure

The mechanism for ototoxicity seems to be at many levels;

- Formation of free radicals within the inner ear
- Toxic effect on stria vascularis and organ of corti
- The OHC's seem to be primarily affected

Carboplatin a second generation analogue of Cisplatin seems to be especially toxic at higher doses and in combination therapy.
The mechanism for ototoxicity is damage to the organ of corti especially the inner hair cells (IHC's).

Nedaplatin has ototoxicity greater than Carboplatin but less than Cisplatin.

Oxaliplatin is a third generation analogue of Cisplatin. It does not seem to have significant ototoxicity but its main side effect is peripheral sensory neuropathy[5].

Iron chelating agents

Deferoxamine is the main compound in this group. It is used mainly for iron intoxication and for iron overload in cases of multiple transfusions.

The mechanism for ototoxicity seems to be from a direct toxic effect on the cochlea and possible effect on higher auditory pathways.

Macrolides

Macrolide antibiotics are in wide use. The most commonly used drugs include erythromycin, azithromycin and clarithromycin.

Erythromycin ototoxicity has been reported in the literature with many reporting reversible toxic effects although irreversible toxicity has also been noted [6].

Risk factors for erythromycin ototoxicity include;

- Renal impairment
- Hepatic impairment
- High serum concentration
- Advanced age
- Female sex

The mechanism for erythromycin ototoxicity seems to be through both from peripheral and central toxicity. Animal studies have shown both hair cell loss and ABR changes.

Azithromycin also reported to be ototoxic but seems to be dose dependent and generally reversible.

Clarithromycin there are few reports in the literature pointing to possible ototoxicity.

Chloramphenicol and Polymyxin

Chloramphenicol is used systemically and topically. Its main side effect is bone marrow suppression. Ototoxicity from systemic administration has been reported and topical preparations have been shown to have significant ototoxicity. These drops therefore should not be used as first line in the presence of tympanic membrane perforation[7].
Of note is the report of two cases of fatal aplastic anemia from topical ophthalmic chloramphenicol drops[8].

Polymyxin is used topically in combination with neomycin and other drugs. There are ten reports of ototoxicity from use of Polymyxin and neomycin topically. Although the risk of polymyxin alone being ototoxic is small it should be used with caution.

Topical Antifungals, Antiseptics and Solvents

Antifungals can be used topically or systemically. There are three main groups; polyenes (amphotericin B, natamycin and nystatin), azoles (clotrimazole, fluconazole, ketaconazole, bifonazole and econazole) and those miscellaneous (toluaftate, polysorbate and potassium sorbate).
Nystatin and **amphotericin B** powder is used as antifungal in the ear. Although not shown to be ototoxic these agents should be used with care in the presence of tympanic membrane perforation.
Clotrimazole powder seems to be free of ototoxicity. **Toluaftate** has a broad spectrum antifungal effect and does not seem to be ototoxic.

Antiseptics are used in many topical antibiotic preparations.
Alcohol when applied to the middle ear causes inflammation, pain and may be ototoxic.

Acetic acid seems to be also ototoxic. Its ototoxicity especially increases when combined with the solvent propylene glycol (Vosol®).

Boric acid is used very widely as antifungal agent topically. Its ototoxicity is unknown.

M- Cresyl acetate solution (Cresylate®) has been shown to be toxic in animals.

Gentian violet has been shown to be very ototoxic in animal studies.

Solvents such as **propylene glycol** are used in many otic preparations. In one antifungal preparation propylene glycol was combined with dexamethasone. Although this is an effective antifungal treatment, propylene glycol has been shown to be ototoxic in animal models[9].

Surgical Disinfectants and Antiseptic

Many surgeons still use disinfectants in the external ear canal prior to ear surgery to reduce the bacterial load. This practice however has not been shown to reduce postoperative infections and may cause significant ototoxicity in the presence of a tympanic membrane perforation. Agents used include;

- Chlorhexidine
- Alcohol
- Iodine
- Quaternary ammonium compounds

Chlorhexidine is used in various preparations for hand washing and skin disinfection. It has been shown to have clear cochlear and vestibular toxicity in animal studies.

Alcohol is used mainly in combination of other agents. There is sufficient evidence for ototoxicity.

Iodine is one of the most commonly used disinfectants and has a low potential for ototoxicity in its aqueous form.

Quaternary ammonium compounds such as cetrimide, best known in combination with Chlorhexidine (Savlon®) has been shown to be ototoxic in animal studies[10].

Monitoring Ototoxicity

There are two elements in monitoring ototoxicity, cochlear and vestibular.

Cochlear Monitoring

- **Basic Audiometry**. It is important and useful but will not detect early changes.
- **High frequency Audiometry** testing threshold above 8000Hz can detect early aminoglycoside and cisplatin ototoxicity.
- **OAE** especially transient OAE's and distortion product OAE's (DPOAEs) can be measured easily and detect early ototoxicity. The measuring device is very portable

and can be used in very sick patients and even comatosed patients. Generally DPOAE's are more sensitive than transient OAEs.

Vestibular Monitoring

- **Electronystagmography (ENG)** tests only the lateral semicircular canal (SCC) and is a test of low frequency vestibular function. It also has a very poor sensitivity in bilateral vestibular loss as might be the case in early systemic ototoxicity.
- **Rotational chair test** allows for high frequency vestibular function to be tested and also allows for differentiation between central and peripheral impairment. It however tests the vestibular apparatus in the horizontal plane only.
- **Computerized dynamic posturography** measures everyday activity and its very useful in rehabilitation. It however does not provide localization of the site of the lesion.
- **Clinical bedside tests**;
  - **Oscillopsia test** is performed by asking the patient to read the lowest line from a Snellen visual acuity chart at rest. The patient's head is then shaken from side to side and the patient asked to read the lowest line that they can read during active head shaking. Missing more than three lines on the chart during active head shaking is generally indicative of a bilateral vestibular loss that might occur from ototoxicity [11]. Normal changes in vestibulocular reflex (VOR) gain should be taken into account as there is reduction in VOR gain with myopic lenses and increase in VOR gain with hyperopic lenses.
  - **The head shake test** is performed by asking the patient to close his or her eyes and passively shaking the patient's head in a horizontal plane back and forth for 20 seconds. The presence of post head shake nystagmus when the patient opens his or her eyes is suggestive for peripheral vestibular dysfunction. The direction of nystagmus is usually away from the affected side but not always. The presence of vertical or rotatory nystagmus after horizontal head shaking is called "cross coupling" and is suggestive of a CNS disorder. The headshake test gives information about asymmetrical vestibular loss.
  - **The Halmagyi horizontal head trust** consists of rapid, passive head movements from each side to midline while the patient visually fixates on a central object such as examiner's nose. Under normal circumstances with rapid head movements there should be an exact equal and opposite movement of the eyes. If there is a defect in the VOR then the eyes lag behind head movement and there will be several corrective saccades required to keep focus on the examiner's nose. Re-fixation saccades should be evident to the examiner[12].

Otoprotective Therapies

Many compounds have been studied for their otoprotective properties especially in relation to the aminoglycoside antibiotics.

- **Alpha- phenyl-tert-butyl-nitrone (PBN)** is a spin trap molecule which can trap and inactivate reactive oxygen species (ROS) when applied to round window membrane.
- **Antioxidants** such as glutathione supplements in the diet of animals have been shown to have otoprotective effect but only when the animal was nutritionally deprived. Studies have shown high levels of glutathione in the OHC's to be protective against toxic effect of aminoglycosides.
- **Methionine** also has antioxidant and metal chelating properties and shown to be otoprotective in animal models.
- **Deferoxamine** as an iron chelating agent has otoprotective effect against ototoxicity of aminoglycosides but unfortunately only at toxic levels.
- **Salicylates** are the most promising otoprotective agents under study.
- **Tanshinone** a traditional Chinese herbal medicine contains diterpene quinines and phenolic acids. They are potent antioxidants and early human trials are promising.
- **Superoxide dismutase** is a naturally occurring antioxidant which has at least in experimental animal otoprotective properties against aminoglycoside ototoxicity.
- **Platinum compound otoprotection** has been shown with thiol compounds, antioxidants, peptides, adenosine receptor agonists and cell death inhibitors. Unfortunately some of these compounds also interfere with the antitumour effect of these drugs[13].

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