OTOTOXICITY

DEFINITION

- Ototoxicity is defined as tendency of certain substances used either systemic or topical, to cause functional impairment and cellular damage to the inner ear, especially to the end organs of cochlea and vestibular divisions of 8th cranial nerve.
- Ototoxic insult may affect hearing or vestibular insult or both depending upon type of chemical and its dose.
- Most important agents to cause irreversible ototoxicity are Aminoglycosides and Cisplatin.

FACTORS INFLUENCING OTOTOXICITY

- Drug concentration in inner ear (Dose, Absorption, Clearance from body, Selectivity to ear)
- Intolerance
- Renal and hepatic disease
- Placental transport (Chloroquine, Streptomycin can lead to ototoxicity in fetus)
- Genetic predisposition.

CLASSIFICATION OF OTOTOXIC DRUGS

<table>
<thead>
<tr>
<th>TOPICAL DRUGS</th>
<th>SYSTEMIC DRUGS</th>
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<tbody>
<tr>
<td>Aminoglycosides – Neomycin, Gentamycin</td>
<td>Antimalarial – Quinine</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Macrolides – Erythromycin</td>
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<tr>
<td>Polymyxin B</td>
<td>Analgesics – Aspirin</td>
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<tr>
<td>Nystatin</td>
<td>Diuretics – Furosemide, ethacrynic acid</td>
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<tr>
<td>Amphoterecin B</td>
<td>Chemotherapeutic agents – Cisplatin, carboplatin</td>
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<tr>
<td></td>
<td>Aminoglycosides – Gentamycin, Kanamycin, Streptomycin etc.</td>
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<td>Polypeptide Antibiotics – Vancomycin</td>
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Other agents that can cause ototoxicity are ➔ Desferrioxamine, Propanolol, Mumps vaccine, Indomethacin, Occupational chemicals (toluene, xylene, and ethyl benzene), metals like lead and mercury, organophosphates.

SITES AFFECTED

- Aminoglycosides ➔ OHC in basal coils of cochlea
- Chemotherapeutic agents ➔ OHC apical ends
- Salicylates and Diuretics ➔ Striae Vascularis

AMINOGLYCOSIDES

- 10% risk of ototoxicity
- Given in cases of sepsis, TB, prevention of secondary infections, cystic fibrosis etc.
- Many aural drops contain it for treatment of Otitis Externa
Use in presence of Tympanic membrane perforation can lead to direct access in inner ear via round window.

PHARMACOKINETICS

- Bioavailability on oral administration is poor and so given systemically.
- Excretion via kidney so in patients with kidney failure, increased concentration may lead to toxicity.
- Clearance from perilymph slower than clearance from serum

SITE OF ACTION

- Sensory neuroepithelium of inner ear i.e. the OHC of basal turns of cochlea. Inner row of OHC affected first and then later outer two layers of OHC. Within the vestibule, the type I hair cells are more susceptible than type II hair cells, and the crista ampulli are more sensitive to toxicity than the utricular or saccular maculae. The pathological findings in the vestibular end organs caused by aminoglycoside ototoxicity often start with a derangement of the sensory hairs resulting in hair fusion creating deformed or so-called ‘giant hairs’. As the damage progresses, the cell bodies change in shape and structure and are often filled with vacuoles and degenerating mitochondria. Loss of the cochlear hair cells leads to secondary degeneration of auditory nerve (Scar formation in the epithelium). INNER HAIR CELLS remain unaffected till frank ototoxicity develops with total destruction of the Organ of Corti.

MOLECULAR PATHOPHYSIOLOGY

- Aminoglycosides bind to Iron metabolite (Fe) to form hydroxyl radical (OH-) that places cell under oxidative stress and causes cellular damage.
- Cell death follows, by apoptosis and necrosis.
- Other cause of cell death include blockade of polyamine synthesis.
- Cochleopathic effect i.e. basal turns of cochlea affected most.
- Damage extends till apex of cochlea as dose increased.
- Labyrinthine injury will usually be gradual, progressive symmetrical bilaterally and permanent but unilateral hearing loss and cases of recovery have been reported.

CLINICAL OTOTOXICITY

- Injury occurs once threshold dose is exceeded. Ototoxic injury progresses much after drug has been stopped.
- Most cochleotoxic aminoglycoside are Gentamycin, amikacin, kanamycin etc.
- HEARING LOSS ➔ High Frequency, Bilateral, Permanent.
- DYSEQUILIBRIUM ➔ Gait Ataxia, Oscillopsia (lack of otolithic input to allow eyes to maintain a level horizon)
- Streptomycin and gentamycin are more vestibulotoxic, usually follows intratympanic gentamycin administration.
- TINNITUS ➔ Initial manifestation of cochlear damage, high frequency
- Others include Vertigo, Nausea, and vomiting, abnormal gait.
- Symptom onset ➔ VTS i.e. Vertigo then Tinnitus then SNHL
- 2 gm/day of streptomycin for 14 days can lead to Vestibulotoxic symptoms.
- **Neomycin** → less oral and topical absorption, cochleotoxic, affects **INNER hair cells > outer hair cells**, kidney elimination
- Kanamycin and tobramycin produces a sloping SNHL which is essentially vestibular sparing (cochleotoxic).
- **MACROLIDE antibiotic – Erythromycin** ototoxicity mechanism is unknown, **reversible** type following cessation of therapy. Doses > 4gm per day have higher risk of ototoxicity.
- Tetracyclines can cause reversible vestibular symptoms.

**POTENTIATORS**

- **Loop diuretics** (Ethacrynic acid or frusemide) potentiate the ototoxicity of aminoglycosides, increase their concentration on scala media.
- Aminoglycoside ototoxicity may occur following either systemic administration, peritoneal dialysis or topical application to the tympanic cavity.
- Transtympanic Gentamycin treatment for Menieres disease → 10% chances of SNHL

**CHEMOTHERAPEUTIC AGENTS**

**AETIOPATHOGENESIS**

- **Cisplatin** is a chemotherapeutic agent effective against solid tumours, including head and neck carcinoma.
- Compared to Aminoglycoside – Similar Type Hearing Loss → *The most frequent pattern of hearing loss is a bilateral, symmetric, progressive, highfrequency sensorineural loss, caused by a loss of cochlear outer, and to a lesser extent inner hair, cells*. Cisplatin also has an action on striae vascularis.
- *The cellular mechanism for ototoxicity is oxidative stress, via an increased intracellular production of reactive oxygen species and free radicals*
- Similar mech. Of apoptosis and necrosis. *More vestibulotoxic than cochleotoxic*

**DIURETICS**

**MECHANISM**

- Inhibition of **cochlear H⁺K⁺ ATPase** causing changes in the electrolyte composition of the endolymph.
- Alteration in hair cell glycolysis

**HISTOLOGY**

- Ethacrynic acid causes destruction of intermediate layer of striae vascularis and outer hair cells of organ of corti (basal turns)
- Clinical ototoxicity → Temporary, VTS (Vertigo, Tinnitus, SNHL)
SALICYLATES LIKE ASPIRIN

- Causes constriction of blood vessels in striae vascularis, spiral ligament and vessels beneath basilar membrane.
- Dose of 6-8gm / day can cause ototoxicity.
- Thus → Streptomycin 2gm/day, Erythromycin 4gm/day and Aspirin 6gm/day can cause ototoxicity.

OTOTOXIC SYNERGISM

If two ototoxic drugs given simultaneously then toxicity can occur even as doses considered within normal limits.

- Eg → Aminoglycosides + loop diuretics.
- Noise exposure and ototoxicity are synergistic according to some studies.

<table>
<thead>
<tr>
<th>class</th>
<th>examples</th>
<th>predominant ototoxic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimalarial</td>
<td>Quinine</td>
<td>Temporary hearing loss, tinnitus</td>
</tr>
<tr>
<td>Analgesia, antipyretics</td>
<td>Aspirin</td>
<td>Temporary hearing loss, tinnitus</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Amikacin, dibekacin, gentamicin, kanamycin,</td>
<td>Permanent hearing loss and/or vestibular injury</td>
</tr>
<tr>
<td></td>
<td>ispamicin, neomycin, netilmicin, paromycin,</td>
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</tr>
<tr>
<td></td>
<td>streptomycin, tobramycin</td>
<td></td>
</tr>
<tr>
<td>Antineoplastics</td>
<td>Cisplatin</td>
<td>Permanent hearing loss and/or vestibular injury</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Ethacrynic acid frusemide (furosemide)</td>
<td>Temporary hearing loss</td>
</tr>
<tr>
<td>Industrial solvents</td>
<td>Toluene, benzene</td>
<td>Permanent hearing loss in animals, inconclusive evidence in man!</td>
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</tr>
<tr>
<td>Polypeptide antibiotics</td>
<td>Viomycin, vancomycin</td>
<td>Permanent vestibular injury, and/or hearing loss</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Erythromycin, azithromycin, clarithromycin</td>
<td>Temporary hearing loss</td>
</tr>
<tr>
<td>Agents for which there have been isolated reports of ototoxicity</td>
<td>Arsenicals, bromides, chloramphenicol, chlorhexidine, erythromycin, mercurials, polymyxinB, tetracycline, vinblastine, vincristine</td>
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MANAGEMENT OF OTOTOXICITY

<table>
<thead>
<tr>
<th>non invasive</th>
<th>invasive</th>
<th>vestibular monitoring :</th>
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<tbody>
<tr>
<td>Basic Audiology</td>
<td>Monitoring cochlear function</td>
<td>ENG i.e. Electronystagmography</td>
</tr>
<tr>
<td>Ultra High frequency Audiology</td>
<td>Endocochlear Potential</td>
<td>Rotational chair test</td>
</tr>
<tr>
<td>BERA – for kids &gt; 3yrs</td>
<td>Cochlear Microphonic Potential</td>
<td>Computerized Dynamic Posturography</td>
</tr>
<tr>
<td>OAE for newborns having inutero exposure</td>
<td>Compound Action Potential</td>
<td>Bedside tests like Oscillosia test, head shake test</td>
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<tr>
<td>Regular serum monitoring of drug concentration</td>
<td>Structural examination of inner ear using light or electron microscopy</td>
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</tbody>
</table>
**COLARADO UNIVERSITY CRITERIA FOR HIGH RISK PATIENTS INCLUDES**

1. Drugs given in presence of renal dysfunction
2. Increased daily doses and for prolonged time
3. High peak or trough levels of drugs
4. Multiple drugs given concurrently
5. Pre existing hearing loss
6. Ear symptoms reported by patients – hearing loss and tinnitus etc.

**TREATMENT OF OTOTOXICITY**

- Drug discontinued after dose titration
- Permanent hearing loss ➔ Hearing AID, Cochlear implant.
- **Cooksey Cawthrone vestibular rehabilitation exercises**
- PREVENTION plays key role.
  - Dose, length of treatment, avoidance in renal failure, hepatic failure, avoided in patients with previous hearing impairment, multiple ototoxic drugs avoided.
- **Antioxidants, Methionine, Superoxide dismutase** have all been tried.
- **Platinum Compound Otoprotection** has been shown with **Thiol Compounds, Antioxidants, Peptides, Adenosine Receptor Agonists and Cell Death Inhibitors.**