

A Review on the Prevention of Aminoglycosides Induced Ototoxicity

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Abstract: Aminoglycosides antibiotics have been in use for a long time. They are bactericidal in nature and are used to treat infections by Gram-negative bacteria. Studies have revealed their dangerous effect on human body that is the Ototoxicity. Aminoglycosides-induced ototoxicity has resulted in permanent hearing loss. Different agents are being examined for their activity against aminoglycosides-induced ototoxicity. These agents govern mostly on the principle of antioxidant capacity.

Keywords: Anti-oxidants; Chelators; Cochlea; Gene therapy; Ototoxicity; Vestibular System.

INTRODUCTION

Diseases or ailments have been lingering with man since his birth. For centuries man has been using various means to treat his diseases. From herbal to therapeutic to chemical, all ways of medication have been explored by the man. This entire quest is for a healthy mind and a healthy body. For it is impossible to imagine human sustainability on this planet Earth without health [1].

Medicine intake is to help your body fight against the disease and overcome it. However exceptions exist as certain medicines leave adverse effects on body. Mostly these effects are minor ones and go unnoticeable but in some cases the effects lead to severe problems such as blindness, hearing impairment, hypersensitivity, etc [2].

Aminoglycosides are among such drugs that cause an adverse effect to the health. These are protein synthesis inhibitors and are mostly used against Gram-negative bacterial infections. They were first naturally derived from *Streptomyces* species but now their semi synthetically produced derivatives also exist [3, 4].

Itchiness, skin rashes, frequent urination, dizziness, etc are the side effects associated with the aminoglycosides but the most dangerous side effect of all is the permanent hearing impairment in the individual. Aminoglycosides are toxic to the ear and results in the development of Ototoxicity. Cochlea and vestibular system are these drugs primary targets. Production of free radicals is the way by which these drugs affect the inner ear and lead to hearing loss [5].

This ototoxicity of aminoglycosides can be treated by the use of different agents whose modes of action are primarily based on their antioxidant capacity. However the molecular based approach is also under study that is the use of gene therapy to combat aminoglycosides-induced ototoxicity [6, 7].

Aminoglycosides

As the name indicates, aminoglycosides are antibiotics that consist of polybasic amino groups in glycosidic linkage with 2 or more amino sugars. They are naturally derived as well as semi synthetically produced. Naturally they are produced from bacteria belonging to *Streptomyces* and *Micromonospora* genus. They were discovered in Waksman laboratory in 1944 from a soil bacterium [8]. They are highly soluble salts of sulfates and exhibit ionization in solution. If taken orally they have poor absorption but are well absorbed in joints and peritoneum. Thus aminoglycosides are mostly administered IV (Fig-1). They are bactericidal in nature and are active against gram-negative bacteria (aerobes and facultative anaerobes) but not against strict anaerobes or gram-positive bacteria. Gentamicin is an aminoglycoside that has been in use against gram-negative bacteria since 1960s [9].

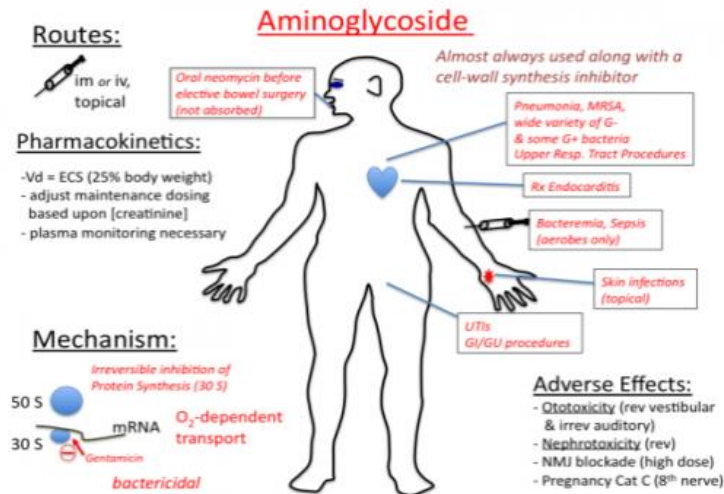


Fig-1: An overview of aminoglycoside

Their mode of action is inhibition of protein synthesis. When aminoglycosides reach the cell wall of prokaryotes, it binds to them and enters the cytosol of prokaryotic cell via active transport mechanism. The antibiotic then attacks the 30S ribosome of prokaryotic

cell (Fig-2) and does not let the formation of initiation complex required for protein synthesis. Aminoglycosides are also found to be the blockers of Krebs cycle energy production. They are excreted in urine [10, 11].

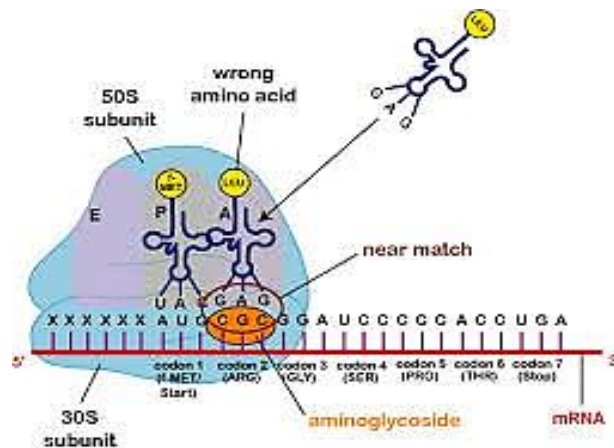


Fig-2: Aminoglycosides Mode of action

As described earlier, their preferred route of administration is parenteral. However some are topically applied and inhaled as well. Gentamicin and Amikacin are given parenteral while tobramycin is inhaled via nebulizer. Neomycin belongs to topical type of aminoglycosides [12, 13].

Aminoglycosides are in use for a long time thus development of resistance against them has been reported. But this resistance is being taken into account by forming various derivatives of aminoglycosides. Moreover in case of severe gram-negative bacterium

infection, aminoglycosides are given along with β -Lactam antibiotics (Broad spectrum) [14].

Ototoxicity

One of the problems most associated with aminoglycosides is ototoxicity that is damage to inner ear resulting in hearing loss. This drug becomes concentrated in labyrinthine fluid and damages the Cochlear and Vestibular region of ear (Fig-3). It has been reported that aminoglycosides while being in inner ear generate free radicals that damages the sensory cells, resulting in permanent hearing impairment [15].

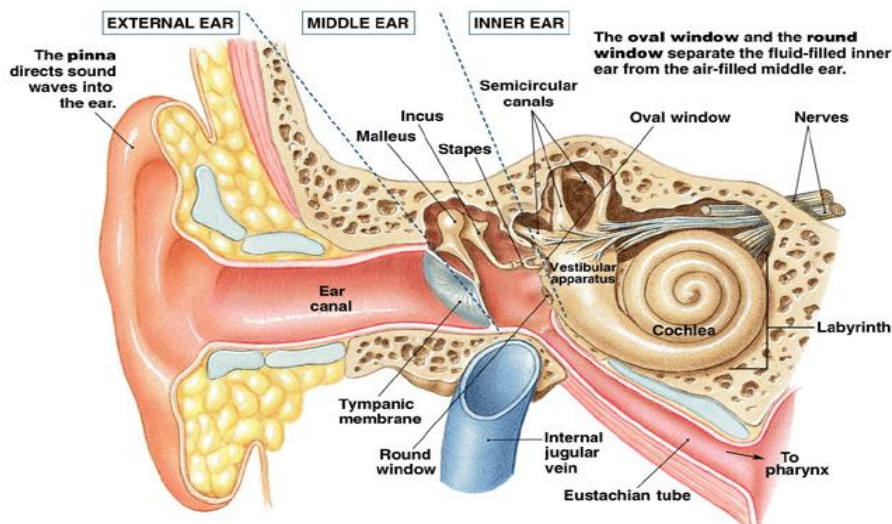


Fig-3: Anatomy of auditory canal

The risk factors for aminoglycosides ototoxicity are [16]:

- High doses of aminoglycosides
- Pre-existing hearing defect
- High blood level of aminoglycosides
- Long therapy (more than 3 days)
- Aging
- Genetic predisposition factor

Prevention of aminoglycosides ototoxicity

The prevention of aminoglycosides ototoxicity is the topic of concern. Different researches are being conducted to find out the solution for this ototoxicity problem. This field of research is a little exploited and much is yet to be explored [17]. As per certain researches:

Salicylate

Gentamicin is an aminoglycoside reported for ototoxicity. Its effects can be altered if Salicylate is used. It is a salt of salicylic acid and acts as an agent against free radicals produced in the case of gentamicin. Salicylates are readily abundant in plants and thus help prevent them against diseases or infections [18].

Chelators and Scavengers

When the metals get excess in the body the Chelation therapy is used. In it Chelating agents are administered into the body and as a result they remove the heavy metals out of body thereby protecting it. Studies have shown that iron Chelators can be used to reverse the effect of ototoxicity. Similarly the free radicals produced in the inner ear can be removed by the use of free radical scavengers (Fig.4). They are antioxidants in nature [19].

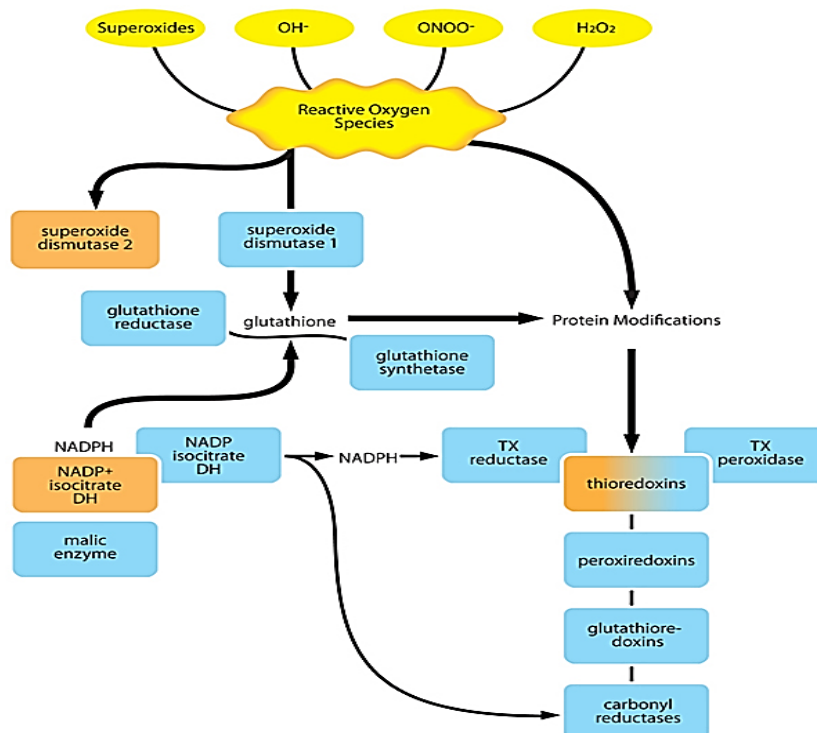


Fig-4: Free radical scavenging pathway

Gene Therapy

The aminoglycosides ototoxicity is said to be related to oxidative stress. Gene therapy can be used to eliminate this problem of oxidative stress (Fig-5). Enzymes such as catalase and Superoxide dismutase (SOD) can be delivered using a vector to the inner ear where these radical scavengers reduce the oxidative stress responsible for ototoxicity. Adeno-viral mediated

gene therapy has been worked on and the results are satisfactory and encouraging to exploit more about the use of gene therapy [20].

Calcium-channel Blockers

Use of blockers for calcium channels has also been reported to prevent ototoxicity but it adversely affects the process of apoptosis [21].

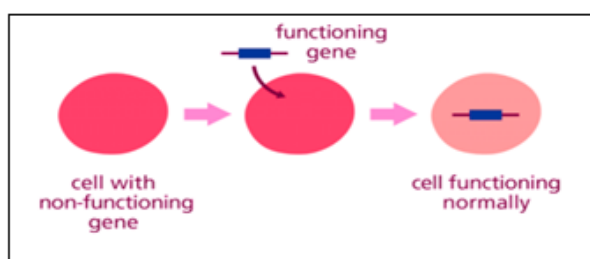


Fig-5: Gene therapy

Alpha Lipoic acid

It is an antioxidant in nature and is an abundant component of Potatoes, Broccoli, Spinach, etc. It exhibits its antioxidant characteristic while combating the aminoglycoside-induced ototoxicity. Structurally alpha-lipoic acid is a thiol compound that is it contains a sulfhydryl group that is carbon bonded [22].

GDNF

It stands for Glial cell line-derived neurotrophic factor and is chemically a protein. Its main function is the promotion of surveillance of different neurons. If this GDNF is pumped to the cochlear region

of ear then it can prevent gentamicin-induced ototoxicity [23].

Lactated Ringer's injection

This injection provides water and promotes hydration. It is also used to provide the body with electrolytes in case of deficiency. Lactate present in it is responsible for the alkalinizing effect. Prevention of ototoxicity by injecting this lactate ringer's solution into the middle ear has been reported [24].

Leupeptin

It is a naturally available protease inhibitor. Protection against gentamicin-induced ototoxicity was

reported when leupeptin was administered in cochlear region of ear [25].

Dexamethasone Injection

It is a corticosteroid which inhibits inflammation in body by preventing the release of inflammation causing substances. It has been reported that if dexamethasone is injected than hearing impairment can be prevented [26, 27].

CONCLUSION

Aminoglycoside-induced ototoxicity can be prevented as well as reverted. Different measures are being taken to avoid this ototoxicity. Most of these preventive measures keep an antioxidant approach towards ototoxicity but the gene therapy is also paving the way for the treatment of ototoxicity. Ongoing researches and researches to be developed in the near future will provide more insight into the ways of preventing aminoglycosides ototoxicity.

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