Research Article

Exploring ototoxicity of aminoglycosides

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Abstract

Any drug with potential to cause toxic reactions to structures of the inner ear, including the cochlea, vestibuler, semicircular canals, is considered ototoxic. The evidence for the ototoxicity of aminoglycoside antibiotics is overwhelming. Drug induced damage to the structures of the auditory and balance system can result in hearing loss, tinnitus and disequibrium. Fetal ototoxicity have been described after maternal exposure to aminoglycoside toxicity, are evaluated. There is susceptibility and genetic predisposition for Aminoglycoside ototoxicity. Relative oxygen species (ROS) participate in the cellular events leading to aminoglycoside induced hearing loss. Monitoring and challenges to hearing loss discussed. Prevention and future prospects explored.
Keywords: Aminoglycosides, Ototoxicity, Fetus, Reactive Oxygen Species, Monitoring Hearing Loss.

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INTRODUCTION

The fact that aminoglycoside antibiotics can produce ototoxicity has been well established in both humans and experimental animals.[1] Otoxicity is referred as tendency of certain agents to cause functional impairment of inner ear. Exogenous ototoxins such as drugs, tobacco and alcohol and 'exogenous ototoxins' such as diabetis and renal disease can cause toxic damage. Ototoxicity may occur in fetus if pregnant mother take exogenous ototoxins.[2] Any drug with the potential to cause toxic reactions to structures of the inner ear, including the cochlea, vestibule, semicircular canals, and otoliths, is considered ototoxic. Drug-induced damage to these structures of the auditory and balance system can result in hearing loss, tinnitus, and dysequilibrium or dizziness[3]

AMINOGLYCOSIDES

This class of drugs is still widely used today. Aminoglycosides may be used in combination with penicillin in staphylococcal, streptococcal, and, especially, enterococcal endocarditis. An aminoglycoside is often added to a beta-lactam antibiotic when serious *Pseudomonas aeruginosa* infections are treated. Aminoglycosides can also be effective in the treatment of tuberculosis. Particular groups of patients, including those with cystic fibrosis, immune dysfunction, and certain chronic infectious disease, are more likely to be treated with this class of antibiotics.[3] Aminoglycosides (AGs) are a well-known and successful class of antibiotics. The initial isolation of streptomycin from Streptomyces griseus provided the long-sought treatment for tuberculosis and an effective antibiotic against gram-negative bacteria. In subsequent years, other AGs were isolated from Streptomyces spp, commonly integrating the ending "-mycin" in their nomenclature. With the isolation of gentamicin from Micromonospora purpureal, the ending "-micin" was implemented to specify the bacterial origin of the individual AG. In contrast to these organic derivatives of soil-dwelling bacteria, synthetic AGs such as amikacin could be developed in vitro. Currently, nine AGs (streptomycin, neomycin, tobramycin, kanamycin, paromomycin, spectinomycin, gentamicin, netilmicin, and amikacin) are approved by the Food and Drug Administration (FDA). In addition to their potent antimicrobial efficacy, all AGs can cause toxic side effects to the kidneys and inner ear. While damage inflicted by AG on the kidney is usually reversible, damage to the inner ear is permanent. This nephro- and ototoxicity was initially discovered in the first clinical trials of streptomycin. Within the inner ear,

streptomycin preferably damages the vestibular organ. Modification of streptomycin to dihydrostreptomycin, however, resulted in a shift of ototoxic damage from the vestibular organ to the cochlea. Generally, each AG is capable of irreversibly damaging both the auditory and vestibular organs, but "typically affects one more than the other". Gentamicin and tobramycin are predominantly vestibulotoxic, whereas neomycin, kanamycin, and amikacin are mainly cochleotoxic. Ototoxic side effects occur within days or weeks after systemic application and are often bilateral in presentation. Vestibulotoxicity occurs in up to 15% of patients after AG administration, whereas cochleotoxicity in 2% to 25% of patients. Different regimens of AG administration and different definitions of ototoxic damage may have contributed to the variation of incidence.[4] Symptoms of cochleotoxicity include hearing loss and/or tinnitus, while those of vestibulotoxicity consist of disequilibrium and dizziness. Unfortunately, these symptoms may not be detected until after the acute phase of severe infection and diagnosis is thus delayed. AG cochleotoxicity typically affects first the high frequency and then extends towards the lower frequency and ranges over time in a dose-dependent manner]. Because the ultrahigh frequencies of hearing are not routinely tested (>8 kHz), the true incidence of AG-induced hearing loss is often underestimated. Indeed, when ultra-high frequency testing was performed, hearing loss was reported in 47% patients with a history of AG treatment.[4]

RISK FACTORS

The following patients are particularly at risk:

1. Bacteremia and fever
2. Hepatic and renal dysfunction
3. Elderly patients above 65 years of age
4. Combination of other ototoxic drugs -Cisplatin, ethacrynic acid and furosemide, amphotericin-B and cyclosporine.
5. Past history of receiving ototoxic agents.
6. Genetic susceptibility5

Susceptibility and Genetic Predisposition for Aminoglycoside Ototoxicity While AGs preferentially target the bacterial ribosome, the inner ear and kidney are known to receive collateral damage in many patients receiving treatment. However, a meta-analysis comparing once versus multiple-daily regimens of different AGs could not determine a statistical significant correlation between ototoxicity and treatment regimens. One main susceptibility factor (17%–33% of patients with reported ototoxic damage is the genetic predisposition to AG ototoxicity. The fact that this increased susceptibility was inherited maternally suggested mitochondrial involvement. Several mutations in mitochondrial DNA are linked to increased susceptibility to AG ototoxicity. Although this genetic susceptibility is present in all organs, the mitochondrial mutations target the cochlea but not the vestibular organs or the kidneys. This is intriguing as this selective cochleotoxicity also occurs with preferably vestibulotoxic AGs such as streptomycin. Exposure to AGs would decrease mitochondrial ATP synthesis resulting in compromised ion pump activity. Reduced ion pump activity in strial intermediate cells could ultimately lead to a progressive decrease of the endocochlear potential. This scenario conceivably explains the slow progression of hearing loss after exposure to AGs observed in patients with increased genetic susceptibility. The strial impairment, furthermore, would explain the little effect on vestibular function in these patients. Interestingly, the stria vascularis demonstrates extensive degeneration in syndromal mitochondrial diseases. This further supports the hypothesis of the stria vascularis as the cochlear cells targeted by the mitochondrial mutations in patients with increased genetic susceptibility to AG ototoxicity. An alternative simple explanation is that susceptibility to the mitochondrial disease is a function of metabolic demand so that hair cells operating at higher frequencies will be more susceptible to a reduced mitochondrial function than lower frequency cells, that is, cochlea versus vestibular, basal versus apical, and type I versus type II. Similarly the highly metabolically active strial cells would also have increased sensitivity. In genetically susceptible individuals, it is postulated that a single injection of AG can cause ototoxic damage], implying that genetic factors can reduce the threshold concentration at which AGs cause damage. At higher concentrations or more frequent doses of AG, the incidence of ototoxic damage exceeds the prevalence of genetic predispositions]. Although in vitro, a clear relationship between damage and AG concentration is observed, the extent of ototoxic damage in vivo does not seem to correlate with AG concentration in targeted tissues. This discrepancy requires further evaluation.4 The oxygen atmosphere under which we live produce a continuous barrage of oxidative damage to all biomolecules. The same reactions creating life may also be responsible for damage due to free radicles. Oxidative stress is a state characterized by an imbalance between pro-oxidant molecules including reactive oxygen species and antioxidant defences.6 Reactive oxygen species (ROS) are a byproduct of normal metabolism and have roles in cell signaling and homeostasis. Species include oxygen radicals and reactive nonradicals. Mechanisms exist that regulate cellular levels of ROS, as their reactive nature may otherwise cause damage to key cellular components including DNA, protein, and lipid. When the cellular antioxidant capacity is exceeded, oxidative stress

can result.7 The presence of AGs within hair cells leads to increased formation of reactive oxygen species (ROS) or free radicals]. A common mechanism for the formation of ROS is the Fenton reaction: Here, the presence of iron salts is required. When gentamicin combines with iron salts, the gentamicin-iron complex enhances iron-catalyzed oxidations and, thereby, directly promotes the formation of ROS. This requires electrons for which unsaturated fatty acids can act as electron donors. In return, those fatty acids, predominantly arachidonic acid, are oxidized to lipid peroxides. As arachidonic acid is an essential fatty acid present in cellular membranes, ROS can affect membrane fluidity and permeability. Via lipid peroxidation, ROS can also affect proteins and nucleic acids thereby disrupting the activity of enzymes, ion channels, and receptors]. ROS naturally occur in the cell as a regular byproduct of cellular metabolism. Normally, the cell protects itself from lethal ROS accumulation with intrinsic antioxidants such as glutathione. This intrinsic protective system is capable of neutralizing ROS to some extent]. When formation of ROS, however, overwhelms the capacity of these intrinsic protective and repair systems, the cell then undergoes apoptotic cell death4 Studies over the last decade have left little doubt that reactive oxygen species (ROS) participate in the cellular events leading to aminoglycoside-induced hearing loss. The evidence ranges from the demonstration of aminoglycoside8

EPIDEMIOLOGY

In certain countries, antibiotics are prescribed freely or are available without prescription. In these areas, aminoglycosides cause as many as 66% of cases of deaf mutism. Depending on agent and dosing, up to 33% of adult patients may have audiometric changes with aminoglycoside treatment. Vestibular toxicity is also well documented; it occurs in as many as 4% of adult patients. The incidence of patients who experience toxicity due to aminoglycosides may be decreasing because of improvements in monitoring and heightened awareness.[3] Since 1950, approximately 50 cases of fetal ototoxicity have been described after maternal exposure to either streptomycin or its congener dihydrostreptomycin. Ten cases of fetal ototoxicity have been described with kanamycin, a related drug. These cases occurred when high doses were used to treat tuberculosis. Gentamicin may be ototoxic to adults and to developing fetuses. Evidence indicates that fetal kidney selectively takes up gentamicin, which can result in cellular damage (probably reversible) to immature nephrons. In addition, inner ear damage or hearing defects have been induced in utero in rats and guinea pigs exposed to streptomycin and/or kanamycin.[9] Studies indicate that cochlear toxicity from aminoglycosides is less common in neonates and children than in adults. Some neonates have had hearing defects, whereas others have had vestibular problems. Some offspring had inner ear damage, whereas others did not[3].

SIGNS AND SYMPTOMS

Clinically, acute cochlear damage may present as tinnitus. Early hearing loss may go unrecognized by the patient and initially manifest as an increase in the threshold of highest frequencies (>4000 Hz). With progression, lower speech frequencies are affected and the patient may become profoundly deaf if the drug is continued. If the drug is stopped early in the course of damage, further loss may be prevented, and partial recovery of auditory thresholds may be possible. However, the loss is usually permanent. Symptoms of vestibular toxicity typically include imbalance and visual symptoms. The imbalance is worse in the dark or in situations in which footing is uncertain. Spinning vertigo is unusual. The visual symptoms, called oscillopsia, occur only when the head is moving. Quick movements of the head are associated with transient visual blurring. This can cause difficulties with seeing signs while driving or recognizing people's faces while walking. Clinically, nystagmus may be present as an early sign.[3]

SPECIFIC AMINOGLYCOSIDES

Streptomycin: Streptomycin was the first clinically applied aminoglycoside and was used successfully against gram negative bacteria in the past. Streptomycin preferentially affects the vestibular system rather than the auditory system. Vestibular damage due to streptomycin is common with prolonged use and in patients with impaired renal function. Because of its toxicity, and because of widespread resistance, this agent is used infrequently today. However, streptomycin use has risen for treatment of tuberculosis.

- Gentamicin: As with streptomycin, gentamicin has a predilection for the vestibular system. Therapeutic peak serum levels of 10-12 mcg/mL are generally considered safe but may still be toxic in some patients. Carefully adjust dosing in patients with renal disease.
- Neomycin: This agent is one of the most cochleotoxic aminoglycosides when administered orally and in high doses; therefore, systemic use generally is not recommended. Neomycin is among the slowest aminoglycosides to clear from the perilymph; consequently, delayed toxicity (1-2 wk) may ensue after discontinuation of therapy. Neomycin is mainly used as an effective otic and ototopical agent. Although neomycin is generally considered safe when used topically in the ear canal or on small

skin lesions, equally effective alternatives are available.

- Kanamycin: Although less toxic than neomycin, kanamycin is quite ototoxic. Kanamycin has a propensity to cause profound cochlear hair cell damage, marked high-frequency hearing loss, and complete deafness. The damaging effect is primarily to the cochlea, while the vestibular system is usually spared injury. Kanamycin has limited clinical use today. As with neomycin, parenteral administration is generally not recommended.
- Amikacin: Amikacin is a derivative of kanamycin and has very little vestibular toxicity. Its adverse effects primarily involve the auditory system; however, it is considered less ototoxic than gentamicin. In the treatment of severe infections, amikacin is mainly indicated on the basis of results of susceptibility tests and patient response.
- Tobramycin: Ototoxicity of tobramycin is similar to that of amikacin; high-frequency hearing loss results. As with kanamycin, vestibular toxicity is less common. Tobramycin is frequently used in otic and topical preparations. Topical use, although not without controversy, is generally considered safe.

Topical Otic Preparations

Certain topical potentially ototoxic drugs that are commonly used in the ear for treatment of acute otitis media (AOM) and chronic suppurative otitis media (CSOM) have recently been evaluated and a consensus position has been presented by the AAO-HNS. The most commonly used ototopical medication is a combination of neomycin-polymyxin. Newer, available ototopical medications are of the class fluoroquinolones, including ciprofloxacin and dexamethasone (Ciprodex) and ofloxacin otic preparations. The following recommendations have been made by the ototopical antibiotic consensus panel (updated 2004)

1. When possible, topical antibiotic preparations free of potential ototoxicity should be used in preference to ototopical preparations that have the potential for otologic injury if the middle ear or mastoid is open. (Aminoglycoside-containing topical drops are not FDA approved for use in the middle ear).
2. If used, potentially ototoxic antibiotic preparation should be used only in infected ears. Use should be discontinued after the infection has resolved. Round window permeability contributes to ototoxic effects. Animal data suggest that the thickened, edematous middle ear mucosa present in an infected ear may provide protection from ototoxicity.
3. If potentially ototoxic antibiotic drops are prescribed for use in the middle ear or mastoid, the patient/parent should be warned of the risk of ototoxicity. And should be instructed to call the physician should dizziness, vertigo, hearing loss, or tinnitus occur. The consensus panel did not feel routine auditory or vestibular monitoring was warranted.
4. If the middle ear and mastoid are intact and closed, then the use of potentially ototoxic preparations present no risk of ototoxic injury.[3]

Monitoring $ CHALLENGES TO HEARING ASSESSMENT

The British Society of Audiology (BSA) provides a standardised guideline for hearing testing in adults and the American Speech-Language-Hearing Association (ASHA) have well-developed guidelines regarding hearing screening for adults and children of different ages. They also provide a guideline for management of individuals receiving cochleotoxic drug therapy. This guideline suggests that testing should be carried out at 250–8,000 Hz at octave intervals, at baseline and, for ototoxic antibiotics, testing should be weekly. Testing should continue until the end of therapy and at 3 and 6 months following discontinuation of treatment. Frequencies 9,000–20,000 Hz can be included to increase sensitivity but this can be time-consuming and the patient may become fatigued. Hearing loss should always be compared to baseline measurements and ototoxicity is defined as any of: 1) a 20 dB decrease at any one frequency, 2) a 10 dB decrease at any two adjacent frequencies or 3) loss of response at three consecutive test frequencies where responses were previously obtained. Ideally, hearing should be tested before any ototoxic drug is given to provide a baseline assessment. In patients with hearing loss at baseline it is still important to regularly monitor their hearing to detect any further deterioration. It is also important to include such patients in research studies At each assessment, otoscopy and tympanometry should be carried out. If the patient is able to cooperate then audiometry should be conducted and in the absence of other international guidelines, the existing ASHA guidelines should be followed.[10] More objective measures of ototoxicity than auditory threshold measurements, such as auditory brain stem evoked response or electrocochleography, have been advocated by some investigators as a better way to make quantitative measurements of auditory function.[1]

Prevention

Efforts in Hair Cell Protection With increasing understanding of ototoxic cell death, a myriad of

therapeutic efforts have been proposed to target various steps of the complex cascades to hair cell death. Those strategies include

- Inhibition of apoptosis,
- Neutralization of ROS
- Administration of neurotrophic factors

Considering that AGs remain in the hair cells for months, potential sustainable regimens would conceivably require long-term treatment. Unfortunately, long-term treatment with anti-apoptotic drugs bears a potential carcinogenic risk, as apoptosis has a crucial primary function in preventing uncontrolled cell proliferation. This carcinogenic risk, therefore, prohibits potential application in human otologic patients. Whether this risk is decreased over a long period by local application to the inner ear remains to be studied. The therapeutic application of anti-apoptotic agents to rescue hair cells after AG exposure has not been reported, but is of further translational interest.

Neutralization of Reactive Oxygen Species

Aminoglycosides form complexes with iron, thereby, catalyzing the formation of ROS]. Competitive blocking of the Fenton reaction involved by iron chelators, thus, is a reasonable approach to avoid oxidative damage from the beginning. Therefore, much efforts aiming at prevention of AG-induced hair cell death have focused on iron. Administration of the iron chelators deferoxamine and[2,3] -dihydroxybenzoate before AG exposure significantly attenuated hearing threshold shifts and protected from hair cell loss in vivo. N-Acetylcysteine (NAC) is another drug commonly used in patients. Beside its mucolytic effect, NAC is also a known antioxidant. In hemodialysis patients who received gentamicin treatment for bacteremia, application of NAC resulted in significantly less high frequency hearing threshold shifts compared to a control group receiving gentamicin alone. Treatment with NAC was continued for one week after cessation of the gentamicin therapy and the protective effects persisted after another six weeks. Compared to ASA (Acytyl Salycylic Acid), NAC does not demonstrate intrinsic ototoxic side effects. A myriad of other agents with known antioxidant capacity has been tested for protection and treatment of AG ototoxicity. These agents are primarily antioxidants such as D-Methionine (D-Met) and α-lipoic acid (α-LA), vitamins such as α-tocopherol (vitamin E) and vitamin C as well as the herbal extracts Gingko biloba] and Danshen]. The hormone melatonin, normally excreted by the pineal gland, also has antioxidant capacity and successfully protected from AG ototoxicity An alternative protective strategy against AG ototoxicity is the upregulation of intrinsic antioxidant mechanisms such as the superoxide dismutase (SOD) Overall, antioxidants attenuate ototoxic damage from AGs. However, the majority of antioxidants did not demonstrate complete protection from AG ototoxicity and effects of long-term treatment remain to be studied.

Management

The primary concern is to maintain patient communication capabilities during what is generally a serious illness. Consult an audiologist early for baseline assessment. Additionally, it is essential to counsel patients and parents regarding the risks of ototoxic medications and emphasize the importance of prompt reporting of symptoms such as tinnitus, hearing loss, oscillopsia, and dysequilibrium. No therapy is currently available to reverse ototoxic damage. Apart from amplification and cochlear implantation, no treatment is available. Therefore, prevention is paramount. High-frequency sounds provide major contributions to speech intelligibility and can therefore have significant effects on communication and listening abilities. When hearing loss occurs, referring patients appropriately for hearing amplification to prevent communication, social, and education set-backs is essential.

DISCUSSION

The evidence for the ototoxicity of aminoglycoside antibiotics is overwhelming, The principal factor preventing reliable estimates of the incidence has been the lack of adequate technology for audiological testing of patients. This includes the lack of availability of high-frequency testing equipment and the lack of development of statistically significant standards of hearing loss in these patients. From a historical perspective, another factor which may confound comparisons between older and more recent data is the progressive change in the management of patients

on these drugs. Today patients receiving aminoglycoside antibiotics are closely monitored, and dosing schedules are changed to match changes in their renal elimination of the drugs. These changes in treatment have been the result of the development of reliable and rapidly performed quantitations of aminoglycoside antibiotic concentrations in blood. Con tribution of oxidative stress to the emerging safety profile of newer drugs remains largely unknown. It is clear that more data are required to provide insight into individual susceptibility to specific ROS-dependent mechanisms of toxicity. Understanding individual differences of this type and the potential for redox effects to manifest as toxicities is increasingly valuable not just for existing therapies but for tailoring clinical drug development. AGs are potent antibiotics with limited application due to their side effects. Until the problem of AG ototoxicity is solved, it is crucial to be judicious in prescribing AGs for defined clinical indications. Furthermore, it is important for clinicians to

remember the genetic mutations as a cause for increased susceptibility to ototoxic damage. However, indiscriminate genetic screening is not cost-effective at present. Instead, a thorough history of the patient and their family regarding ototoxic symptoms from antibiotics helps assessing the individual risk. Independent from genetic mutations, patients should undergo a baseline hearing test including ultrahigh frequencies prior to AG administration to allow for early and unambiguous assessment of potential ototoxic damage. Aminoglycosides are cleared more slowly from inner ear fluids than from serum and therefore a latency exists to the ototoxic affects of aminoglycosides. This latency can result in progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment. Continuing to monitor the patient for cochleotoxic and vestibulotoxic effects up to 6 months after cessation of aminoglycoside treatment is important. Clinicians must carry out a risk assessment whereby the risk of hearing loss is weighed against the risk of treatment failure from stopping or not using an injectable drug. Patients need to be informed of the risks of treatment and the risks of not using injectables and permitted input into treatment decisions. New, alternative drugs are urgently needed. Scientists and clinicians are continually seeking to find new methods to minimize ototoxic injury while retaining the therapeutic efficacy of these agents.

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