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THERAPEUTICAL PRACTICE

AMINOGLYCOSIDE-INDUCED DESTRUCTION OF THE COCHLEA

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Abstract. The inner ear houses the hearing organ of Corti (inner and outer hair cells), where the sound pressure is transduced to electrical energy. The inner and outer hair cells both play active roles in this transduction.
Drugs' ototoxicity is defined as functional and/or anatomical impairment of the inner ear caused by certain therapeutic agents.
Aminoglycosides are widely prescribed despite their toxicity, because of their availability, good spectrum and low cost. These antibiotics cause hearing loss, starting with high frequencies and progressing toward conversational frequencies (0.5-2 kHz), by destroying the acoustic hair cells in the inner ear.
The hearing loss is often irreversible and bilateral. In neonates, aminoglycoside ototoxicity is more severe, causing profound bilateral hearing loss (all frequencies are affected) which will impede language development.
The management of cochlear toxicity entails monitoring, appropriate schedules of therapy, association of presumed protectors and in extremis referral to the ENT specialists for cochlear implant.
Keywords: antibiotics, aminoglycoside, cochlear toxicity

Review of Inner Ear Anatomy and Physiology

The human cochlea is a spiral structure with a length of about 35 mm, which swivels two and three-quarters times and has three fluid-filled compartments (scalae) [1,2] The scala media houses the Corti organ (hearing organ), that lies on the basilar membrane. It consists of outer hair cells (OHC), inner hair cells (IHC), supporting cells and the tectorial membrane.

The mechanical wave of sound passes through the outer ear, middle ear to the inner ear. The vibrations are then transmitted via the inner ear's liquids as travelling waves along the basilar membrane. At the point of maximal displacement of the basilar membrane, a stimulation of the Corti organ appears and the sharp mechanical energy amplified by the OHC is converted into electrical energy by the IHC, passing further as auditory signal towards the brain. Stimulation of the organ of Corti takes place tonotopically, depending on reaching the travelling wave's peak: the high frequencies sounds are perceived at the base of the cochlea and the lower frequencies sounds are perceived progressively closer to the apex.

A clear perception of a sound (very good sen-

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sitivity and frequency selectivity) depends on the anatomical integrity and well as on the functioning of the cochlear amplifier, represented by the outer hair cells[3]. OHC is the level where ototoxic drugs mainly act (Figure 1).

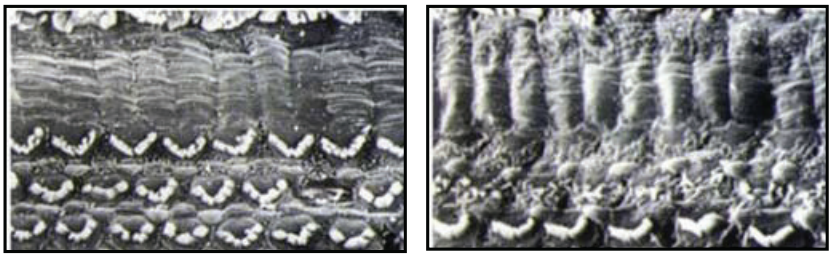

Figure 1. 3 rows of "V"-like arranged cilia of normal OHC (left) and damaged OHC's cilia - only one row is still visible (right) **(***kindly supplied by Dr Andrew Forge of the Institute of Laryngology and Otology, University College, London)*

Aminoglycosides

Aminoglycosides (AG) are antibiotics active against a lot of aerobic Gram- negative microorganisms (including multidrug–resistant non-fermentive rods), Gram- positive microorganisms (including listeria and resistant cocci) and against *Mycobacterium tuberculosis*.

AG are highly effective and inexpensive antibiotics, which contributes to their frequent use worldwide.

The class includes several groups: streptomycin, the kanamycin group (kanamycin, tobramycin, amikacin); the gentamicin group (gentamicin, netilmicin, sisomicin) and the neomycin group (neomycin, paromomycin).

Aminoglycosides are not absorbed from the gastrointestinal tract, because of their large molecule, polycationic polar structure, so they must be administered parenterally for systemic effect, or, for local effect - topically (ear drops, peritoneal lavage, ointment applied to burns), intratympanically, intrathecally, orally (bowel preparations).

AG are excreted unaltered by the kidneys, where they concentrate very well. Due to the fact that their therapeutic index is narrow, any impairment of the renal function leads to increased toxicity.

The mechanism of antimicrobial action consists in blocking bacterial protein synthesis (ribosomal 30 S subunit).

AG are bactericidal, concentration-dependent antibiotics, with an important postantibiotic effect (PAE) of several hours (which allows continued efficacy even when serum concentrations fall below the expected minimum inhibitory concentrations) [4,5]

AG ototoxicity

AG are well-documented ototoxic and nephrotoxic drugs, probably because of their concentration in, and retention by, the sensory hair cells of the cochleovestibular and renal proximal tubule cells.

Ototoxicity is defined as the tendency of certain therapeutic agents to cause functional impairment and cellular degeneration of the inner ear. It is differentiated from neurotoxicity where the site of action is central to the eighth cranial nerve (auditory cortex).

The incidence of aminoglycoside ototoxicity is reported in a large range, varying from 2% to 41% in different studies [6,7,8,9] and involves both cochlear and vestibular systems, in variable degree, depending on the drug: streptomycin and gentamicin seem to be more vestibulotoxic whereas amikacin, kanamycin and neomycin are more cochleotoxic [10]. Because of their high acoustic toxicity, the use of neomycin and kanamycin is limited today. This differential ototoxicity depends to some extent on the number of the free amino or methylamine groups attached to the glycoside portion of the molecule [11].

Risk factors for aminoglycoside ototoxicity include: long course of therapy, elevated serum levels (high dose, multiple doses regimen or impaired renal function), concomitant use of other ototoxic agents (loop diuretics, platinum-based antineoplastic agents, other antibiotics: glycopeptides, macrolides), prior aminoglycosides exposure, noise exposure, use in neonates and genetic factors. There appears to be a genetic predisposition to developing aminoglycoside ototoxicity. The A1555G mutation in the mitochondrial small ribosomal RNA gene (12S rRNA) has been associated with aminoglycoside-induced hearing loss [12]. Additional mutations are also being investigated. It could be useful to

add a question to the anamnesis of any patient before receiving AG, about familial drug-induced hearing loss.

The antibiotics are rapidly taken up into the hair cells related to cationic-selective channels (particularly TRP channels) [13] and by classical endocytosis. The high degree of uptake in the hair cells seems to be directly related to toxicity manifestation at that level. First hair stiffness appears then anatomic destruction of the whole cell.

The exact mechanism of cellular damage is not entirely clear. It seems to be an injury of the mitochondrial membrane and mitochondrial RNA [9,13,14], with subsequent formation of reactive oxygen species and initiation of cellular apoptosis [9,15,16, 17, 18].

Morphologic studies demonstrate that the inner row of outer hair cells (OHC) of the basal turn of the cochlea are affected first, followed by the other two rows of OHC and the inner hair cells [10].

Patients frequently develop symptoms during the final days of therapy or following the cessation of the treatment (studies on animals demonstrate the presence of aminoglycosides molecules in hair cells up to six months after administration [13,19]). The hearing loss begins with high frequencies and progresses to lower frequencies. [9,20]. It is often bilateral and irreversible.

Ototoxicity in Infants

The infection is the most common cause of infant and child mortality worldwide [21]. As there is such overlapping of the clinical presentations of bacterial infection, an empirical combination of antibiotics is often used to cover the most common pathogens. Gentamicin is relatively cheap and widely available and is bactericidal against most aerobic Gram-negative and some Gram-positive organisms: as a result, it is often included in empirical treatments and in the first line treatment for sepsis in the neonate.

The starting dose and dosage interval of gentamicin are usually based on the infant's weight and gestation [22,23,24]. Over the last decade, there has been a shift from giving the drug every 12 hours in the term infant, to giving a larger dose every 24 hours [22,25,26,27].

Neonates have a longer half life for gentamicin than adults [28](in adults there is a half time of 2,5 hours [4]) and in the very preterm infant it may be prolonged to 14 hours [29]. Therefore neonates require a longer dosage interval compared to older children and adults, and preterm neonates require even longer dosage intervals. More than that, risk factors for ototoxicity have to be defined: reduced creatinine clearance, raised serum creatinine or β-2-microglobulinuria [27].

Very important are the functional consequences of AG induced ototoxicity which are much more severe in infants than in adults. If adults develop high-frequency induced hearing loss, in infants lesions occur simultaneous on the entire length of the cochlea and all frequencies are affected (profound sensorineural hearing loss).

Managing the AG ototoxicity

The management of cochlear toxicity entails appropriate schedules of therapy, association of presumed protectors, monitoring and referral to the ENT specialists if requiring cochlear implant.

Protection against AG ototoxicity

Dosing regimens have been examined in order to establish the relation with efficacy and toxicity for the classical schedule - multiple daily dosing (MDD) versus the once-daily dosing (ODD) schedule. For once-daily therapy (ODD) plead the aminoglycosides' characteristics (concentration-dependent bactericidal activity and long postantibiotic effect), decreased risk of emerging resistance, and decreased accumulation in the inner ear and renal tissue. Two metaanalyses, including 24 studies (995 patients), respectively 4 studies (328 patients) establish that there is no significant difference between ODD versus MDD concerning clinical and microbiological efficacy, but there is an important trend that favours ODD. Besides, the nephrotoxicity seems to be lower with ODD. Ototoxicity remains similar [30,31].

There is significant research effort to prevent AG ototoxicity. Partial protection is obtained by substances which inhibit mitochondrial permeability and diminish the oxidative stress of the hair cells (antioxidants): iron-chelators, cyclosporine A, glutathione, salicylates, erythropoietin, glial cell line-derived neurotrophic factor (GDNF), fosfomycin, lipoic acid, N-acetylcysteine, D-methionine [32,33,34]. Intratympanic administration of these agents appears to enhance their protective effect.

Gene therapy is also being investigated for generating new functional hearing cells and is the subject of intensive research [35].

Monitoring AG toxicity

OHC damage can be monitored by an audiology

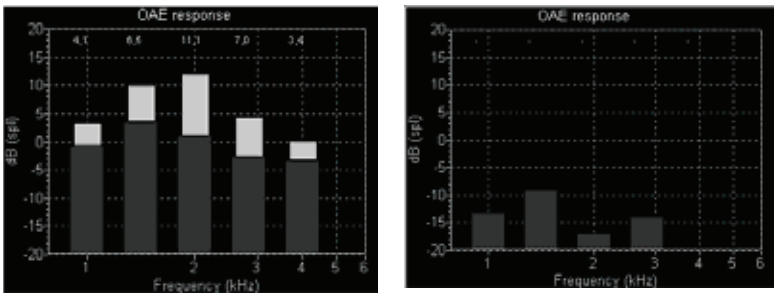

Figure 2. Otoacoustic Emissions present in normal inner ear (in blue) (left) and absent in damaged outer hair cells (right) *(personal data base)*

test (otoacoustic emissions). Otoacoustic emissions (OAEs) are small sounds generated by the motion of the outer hair cells, which can be recorded by a microphone fitted into the ear canal. OAEs' recording represents a simple, non-invasive, very sensitive and specific tool for screening cochlear function that can be used to monitor the effects of ototoxic treatment and allows right medical decision when cochlear damage appears [3,36] (Figure 2).

Monitoring AG treatment using OAE analysers can be very useful for the detection of early auditory dysfunction, because it provides information about high frequency ototoxicity prior to aminoglycoside toxicity in conversational frequencies.

Cochlear Implant

Sensorineural deafness in infants is not obvious and its active diagnosis should be done, otherwise language development is not possible and deaf children will have a double handicap – they will be deaf and mute as well. Universal newborn hearing screening is the precise tool for identifying infants with hearing loss and the same appropriate equipment can also be used in neonates for monitoring AG induced hearing loss.

Once deafness is diagnosed, early appropriate intervention is required. For children with profound bilateral hearing loss, cochlear implant is the only current solution.

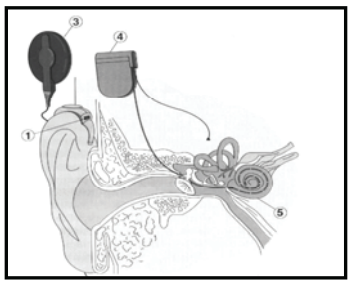

Figure 3. Cochlear Implant **(***with permission of the Hearing Implant Company)*

Cochlear implant is a semi-implantable hearing aid designed to shortcut the damaged ear. It has the possibility to receive environmental sounds and voice, to digitise them and to transmit them directly to the auditory nerve (Figure 3).

If cochlear implantation for appropriate deaf children is carried out around the age of 2, the verbal development of the children is similar with that of their normal hearing peers. As time passes prior to cochlear implantation, children will never be able to make up for the time difference in language development compared with matched pairs. Cochlear implantation after the age of 7 will have no benefit in auditory and language rehabilitation, since the auditory cortex is not able to receive any more information from the auditory nerve. [37]

Conclusions

Although ototoxic medications play important roles in modern medicine, they also have the capacity of doing great harm and producing significant morbidity. Physicians have to be aware of this specific pathology, in order to identify patients who are at great risk for developing ototoxicity and to give an early diagnostic of cochlear damage induced by AG.

Ototoxicity is recognised, but some medical conditions require aminoglycoside therapy. Precautions should be taken regarding the appropriate administration (dosage, administration regimen, without dangerous associations – e.g. loop diuretics) and the monitoring of any auditory impairment that can occur.

Though some otoprotective substances are being successfully used in certain studies, further trials must be performed to asses their clinical utility.

A gene therapy for induced-hearing loss is currently being investigated and the results are very promising.

Until these under-researched treatments are available, the cochlear implant remains the only

valuable treatment for deaf children who needed ototoxic treatment for different pathologic conditions.

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