The Prevention of Ototoxicity in Developing Countries

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Ototoxicity is a major preventable cause of hearing loss in the developing world which disproportionately affects children.[1] In this chapter, we will explore the issues related to ototoxicity and its prevention. In theory, ototoxic hearing loss should be easy to prevent. Since the injury is generally caused by health professionals, merely eliminating the use of ototoxic medications would eliminate this relatively common cause of hearing loss. Yet, in reality, the pathophysiology and public health issues related to ototoxicity are quite complex.

To better develop a prevention strategy for ototoxicity we need to better define the causative factors. We begin by comparing some of the substances that are known to be ototoxic according to the degree of ototoxicity and the populations at risk. A comparison of these features for many potentially ototoxic agents is shown in (**Table 1**).

Table 1. Ototoxic Risk of Various Substances and Population Exposed to Risk

	Ototoxic Risk	**Exposed Population**
Aminoglycosides	High	High
Vancomycin	Low	Low* *increased w/MRSA?
Loop Diuretics	Low	Moderate
Salicylates	Low	High
Cisplatin	High	Low
Chloroquine	Unknown	High
Industrial Chemicals	High	Unknown

As we compare these substances, we see that most of them have either a relatively low rate of ototoxicity or a relatively small percentage of people at risk. Of these substances, aminoglycoside antibiotics are the most concerning because

they are highly toxic to the inner ear and are widely used. This combination puts a large population of people in the world are at risk and we will, therefore, devote most of this chapter to a discussion of aminoglycoside ototoxicity.

Aminoglycoside Toxicity

Although exact incidence figures are unknown, it is estimated that cochlear or vestibular toxicity occurs in 1-5% of patients exposed to these medications.[2] Hearing loss is initially in the high frequencies, and may be detected by audiometry before the hearing loss becomes apparent to the patient. Loss of vestibular function can be completely independent of hearing loss, and the patient may be unaware of a balance problem due to visual or central brain compensation mechanisms. Cochlear and/or vestibular damage can occur with any of the different aminoglycoside antibiotics. While all aminoglycosides can cause either cochlear and/or vestibular damage, there are differences in the toxicity potential. For example, the order of auditory toxicity of five aminoglycosides, from most to least, is neomycin, gentamicin, tobramycin, amikacin, and finally netilmicin.[3] When an aminoglycoside antibiotic must be used, it is preferable to consider the least toxic drug possible, all other things being equal. Unfortunately, these less toxic drugs are more expensive and cost factors frequently dictate which aminoglycosides are available in a developing country.

Four major factors influence aminoglycoside ototoxicity in the developing world: increased exposure to the drug, sicker patients with higher co-morbidity factors, genetic susceptibility to the drug, and unregulated or inappropriate use. With the recent advent of safer broad spectrum antibiotics, most practitioners in the industrial world have seen a dramatic decrease in the use of aminoglycosides in recent years. A program that tracks drug use in the United States documented a 50% reduction in aminoglycoside use from 1999 to 2001.[4] Likewise, ototoxicity appears to be a relatively uncommon cause of deafness in several large studies in industrialized nations as shown in (**Table 2.**)[5-9]

Table 2. Proportion of Ototoxicity in Deaf Populations: Industrialized Nations

Country	**% of Deaf**
Italy[1]	1.9%
Belgium[7]	0.6%
Germany[5]	2.2%
Puerto Rico[8]	1%
Portuguese	1.7 %
Multi-national / Meta-analysis[9]	<1%

It is safe to say that aminoglycoside toxicity is relatively uncommon in these developed countries, due in large part to lack of exposure. Aminoglycosides do continue to be utilized in certain populations. For example, they are still given to 21% of children in the Pediatric and Neonatal Intensive Care Units as reported in a study from the United States.[10]

A major concern is the high rate of aminoglycoside use in developing countries, due to their low cost and broad spectrum.[11] Aminoglycosides continue to be used both appropriately and inappropriately in these settings. This higher level of use in some parts of the world has been documented in several studies. They accounted for 7.4% of all antibiotic prescriptions in one study in Russia and 11% of those in Trinadad.[12-13] A study comparing aminoglycoside use in Hong Kong documented utilization that was 250 times that in Great Britain during a similar time period.[14] Likewise, some areas of the world have recorded much higher rates of aminoglycoside toxicity and/or exposure in deaf populations. The highest incidence of aminoglycoside ototoxicity has been in China, where studies of deaf populations have indicated a rate of aminoglycoside toxicity ranging from 3.7% to as high as 28.4%.[15-16] Studies in East Africa have also shown higher rates of ototoxicity and our study in Nicaragua documented gentamicin exposure in 31% of deaf children.[17-18] These higher rates are presumed to be in part due to increased exposure.

In addition to increased population exposure, other factors may be contributing to these elevated rates. Some of the factors that are known to increase the risk of ototoxicity from aminoglycoside use include: duration of therapy, frequency of dosing (with less toxicity in daily dosing schedules), kidney or liver dysfunction, advanced age, simultaneous use of other ototoxic medications (especially the loop diuretics), higher serum concentrations, more severe infections, and, lastly, a genetic predisposition. [2, 20, 21] Due to lack of regulation and poor health care in general, several of these factors may be more prevalent in poorly developed areas of the world.

A major breakthrough in the prevention of aminoglycoside ototoxicity came from an observation by Sha and Schacht that anti-oxidant treatment with salicylates protected hair cells of guinea pigs exposed to gentamicin.[22] This same research team subsequently published a large blinded, placebo-controlled clinical study with a group in China that looked at the clinical effectiveness of aspirin administration in the protection of patients from gentamicin ototoxicity.[23] Only 3% of the 89 patients who received 3 grams per day of aspirin along with their gentamicin had audiometric evidence of ototoxicity, which was significantly reduced from the 13% in the placebo group. This is an excellent example of basic science research translating to a clinical tool that will potentially impact the onset of hearing loss in the world. Unfortunately, the appropriate dose and safety of this intervention has not been studied in newborns, the population at greatest risk.

A second major breakthrough in our understanding of aminoglycoside totoxicity came from two independent research teams that each identified large families with an increased susceptibility to aminoglycoside ototoxicity that was inherited from the mother.[24-25] Further studies have identified the gene in these families to be located on the mitochondrial DNA in the cell, which is inherited from the mother in both males and females. In particular, the mutations that increase aminoglycoside ototoxicity are located in that part of the DNA that codes for the 12S subunit of the ribosomal RNA. This ribosomal subunit shares a homology with the ribosomal units of bacteria. These mutations change the structure of the

human ribosomal unit to more closely resemble the bacterial ribosome. These mutated ribosomal structures are more susceptible to aminoglycosides with a resulting disruption of protein synthesis. There are several mutations that have been identified in patients with aminoglycoside ototoxicity. The most common of these overall is the A1555G mutation, but other mutations are more common in some populations.[26-29]

An important concept in understanding the role of mitochondrial mutations and hearing loss is that some patients with these mutations will eventually develop a progressive non-syndromic hearing loss independent of aminoglycoside exposure. The probability of hearing loss with the A1555G mitochondrial mutation is highest for those patients given aminoglycosides, yet those patients who did not receive aminoglycosides still developed hearing loss, although milder and later than the exposed group.[30-31]

To better understand the prevalence and difficulty in studying aminoglycoside ototoxicity in developing countries, we studied a group of patients in Nicaragua with childhood hearing loss. In this study of 96 patients, we found that 31 patients (32%) had a history of gentamicin exposure that coincided with their hearing loss.[32] Although some of these patients did have a family history of hearing loss, none of them were found to have mutations in the 12S ribosomal RNA mitochondrial gene. Although the patients with gentamicin exposure seemed to be geographically clustered, we felt that this distribution may represent increased availability of the drug in these regions. One of the complicating factors in assessing hearing loss in this population is the high prevalence of multiple risk factors. Although gentamicin exposure is high, this risk factor overlapped with a history of meningitis and perinatal distress.

We have seen how aminoglycosides are more widely used in some areas, ototoxicity in general and genetic susceptibility is more common in some populations, and patients in developing countries are more likely to have other comorbid factors. Unfortunately, most of these factors are difficult to control. One area were public health initiatives are likely to have an impact is by limiting the inappropriate and unregulated use of the drug. It is important for us to first recognize that aminoglycosides have an important role in the treatment of severe life-threatening infections. Neonatal sepsis, for example, accounts for an estimated 1.6 million deaths each year in developing countries.[33] Many of these deaths can be prevented while minimizing the toxic risk of the drug through extended interval dosing. Studies in India and elsewhere have recently shown that neonatal sepsis can be safely and effectively treated with a straightforward dosing regimen of gentamicin.[20] Aminoglycosides are also important tools in the treatment of tuberculosis. The rising incidence of tuberculosis, multiple drug resistant tuberculosis and the subsequent use of potentially ototoxic drugs in the treatment of it is a good example of how we are unable to separate ourselves from the world around us. Tuberculosis is still much more prevalent outside of the U.S., but drug resistant tuberculosis is a problem that we face in the United States as well.

Aside from these appropriate uses of the drug, gentamicin is often given in settings that are poorly controlled and may not even involve a physician. In spite of

regulations that prohibit dispensing medications without a prescription, gentamicin injections can be obtained directly through pharmacies in Nicaragua and other developing countries. Studies in Bangladesh and Venezuela have shown that over 90% of antibiotics are dispensed this way.[34,35] Outpatient use of gentamicin, often without a physician's prescription, has also been demonstrated to be common in India and Hong Kong.[14,36] Finally, studies have found that even when physicians are involved with prescribing aminoglycosides, the dose and or indications are often inappropriate. An audit of one Indian children's hospital discovered that nearly 30% of inpatient aminoglycoside use was inappropriate either in the indication or dose.[36] High rates of gentamicin ototoxicity in these populations, therefore, may be due to high exposure to the drug or inappropriate doses. Although there have been few studies to document antibiotic use or regulation in Central America, studies demonstrating a reduction of inappropriate aminoglycoside prescriptions have been shown after interventions in Columbia.[37] The widespread, unregulated use of gentamicin appears to still be a major problem in most developing countries and control of this problem is compounded when these drugs are dispensed without the involvement of a physician. In addition to the widespread and unregulated use, poor health care in developing countries may lead to a delay in treatment and result in more severe infections and an increased risk of ototoxicity.

In summary, the prevention of aminoglycoside ototoxicity depends upon the ability to regulate its use and educate providers about ototoxicity. If possible, less toxic alternatives should be provided. Finally, the co-administration of aspirin has shown great promise in preventing hearing loss when an aminoglycoside must be used.

Vancomycin Toxicity

In contrast to aminoglycosides, vancomycin is less commonly used worldwide and certainly less toxic. Despite the similarity of names, vancomycin is not an aminoglycoside. The toxic effect of vancomycin alone on the inner ear is somewhat controversial. Vancomycin may potentiate the toxicity of aminoglycosides and does appear to have an ototoxic effect of its own when given at high dose for prolonged periods of time.[2-3,38]

Loop Diuretics Toxicity

Another class of ototoxic medications are the loop diuretics, with the most common being furosemide and ethacrynic acid. These diuretics have relatively low toxicity and moderate to low percent of the population at risk. Despite this fact, loop diuretics were the second most common cause of ototoxicity in a Nigerian teaching hospital.[39] The mechanism of ototoxicity does not appear to be hair cell damage, but rather reversible reductions in endocochlear potential, electrolyte changes in cochlear fluids, and histologic changes in the stria vascularis. These are changes that could be predicted from the action of diuretics on fluid balance in the kidney and other parts of the body. The greatest risk of ototoxicity is in premature infants, patients with renal impairment, and in the concomitant use of another ototoxic medication, most notably aminoglycosides.[2-3]

With loop diuretics, the hearing loss can be either permanent or reversible, and after either oral or intravenous administration. The biggest demonstrated

risk of furosemide is with a rapid intravenous administration (greater than 5 milligrams per minute). The clinician should be aware of bumetanide, which has comparable effects to furosemide, but is less toxic. It is an alternative for patients at higher risk of ototoxicity, but is more expensive.

Salicylate and NSAID Toxicity

Although we have already seen how aspirin can play an important role in the prevention of aminoglycoside ototoxicity, paradoxically salicylates may be ototoxic themselves. Salicylates are commonly used for their anti-inflammatory, antipyretic, analgesic, and anti-platelet effects. The toxic effect to the auditory system is usually a mild to moderate, bilaterally symmetrical sensorineural hearing loss, which is usually reversible within 24 to 72 hours after cessation of the drug. It can be accompanied by high-pitched tinnitus, which may be the initial symptom of ototoxicity, and is also usually reversible. The audiogram may show a flat or high frequency hearing loss. Salicylates rapidly enter all areas of the cochlea. The toxic effect of salicylates seems to be more a biochemical effect without significant changes in the hair cells of the cochlea. For monitoring purposes, the ototoxicity seems to be correlated more with unbound serum levels than total serum levels. Nonsteroidal anti-inflammatory drugs, or "NSAIDs", are analgesic and anti-inflammatory medications that inhibit the cyclooxygenase pathway, and have a similar hearing loss effect, and reversibility, as aspirin. [2,3,40]

Cisplatin

The next class of ototoxic medication that we will discuss is chemotherapy agents, and the prototype ototoxic medication is cisplatin. Although chemotherapeutic agents like cisplatin are highly ototoxic, the exposed population to these drugs is thankfully low. The side effects of cisplatin, in general, include nausea and vomiting, nephropathy, and neurotoxicity. Neurotoxicity can include peripheral sensory neuropathy, autonomic neuropathy, and high frequency sensorineural hearing loss.

Although a bilateral, high frequency, symmetrical sensorineural loss is initially found, the hearing loss progresses to the lower frequencies with a higher cumulative dose. The loss is permanent, and tinnitus is common. The incidence of hearing loss is high, estimated at 50% of patients, and is dose dependent, usually with a cumulative dose of greater than 200 milligrams. [2,3,41]

Since cisplatin presents first with a high frequency loss, ultra high frequency audiometry may detect early ototoxicity, and allow modification of treatment protocols. This monitoring is most effective if an initial baseline ultra high frequency audiogram can be obtained prior to treatment. Histologic damage is seen in the stria vascularis, spiral ganglion cells, and outer hair cells of the cochlea. As damage progresses, cochlear inner hair cells are involved. Carboplatin, a second-generation analog, is more toxic initially to the inner hair cells, than cisplatin. Fortunately, cisplatin toxicity is mainly cochlear, and not vestibular. The co-administration of certain agents may protect the ear against cisplatin toxicity. Many drugs have been investigated in this regard including D-Methionine, N-acetyl cysteine, thiosulfate, intratympanic steroids, and intratympanic lactated Ringer's solution.[42]

Chloroquine Toxicity

Because of the high incidence of malaria in some areas of the world, chloroquine ototoxicity is mostly a concern for developing countries. It is estimated that 300 – 500 million people are infected with malaria each year and it is unknown exactly how many of these are treated and with what medications. In some areas of sub-Saharan Africa malaria or the treatment of malaria accounts for nearly one third of all cases of deafness. It has been proposed that quinine may cause a reversible hearing loss and tinnitus, similar to aspirin and NSAIDs.[36] It may also cause vestibular symptoms. Auditory Brainstem Response (ABR) may be an sensitive method of early detection. The mechanism of ototoxicity is unknown, but the outer hair cells seem to be the site of action. Quinine still is used as an alternative medication for malaria, and commonly used for leg cramps, although efficacy is unproven.[43]

Heavy Metal and Industrial Toxicity

Heavy metal and industrial chemical toxicity seem to be much more common in the developing world where the use of these substances is not well controlled or regulated. In communities with mining or industrial activity, workers and their families may be exposed to these substances. In addition to the ototoxic effect alone, some industrial toxins may facilitate the noise induced hearing loss that often accompanies their exposure in industrial settings. Very little research is done on the effect of these substances specifically on hearing. Heavy metals, such as mercury, arsenic, and lead have been implicated in hearing loss from either exposure during gestation, post natal development or as an adult.[44-49] The ototoxic effect of these metals is somewhat controversial and in some cases the ABR may show a prolonged I-V interval; therefore, therefore, the ”ototoxicity” of these substances may be due to more central effects on the auditory nerve or brainstem.[50] As such, monitoring changes in the ABR may detect toxicity earlier.

Some industrial toxins that are known or suspected to aggravate noise induced hearing loss include the organic solvents toluene (used in printing and wood finishing), methylbenzene, and styrene (used in plastics industry). In addition, asphyxiants, such as carbon monoxide (due to poor ventilation in the workplace) and hydrogen cyanide (found in metal and fabric processing as well as cigarette smoke) increase the susceptibility to noise. Some metals such as lead (found in paint) and mercury (found in industry and fish) may also potentate noise induced hearing loss. Finally, the pesticides paraquat and organophosphates may increase the susceptibility to noise exposure. [44]

Ototoxicity Prevention

There are several issues to consider before treatment with an ototoxic medication. It is important to search for a history of prior ototoxicity, renal or liver dysfunction, and a family history of aminoglycoside induced hearing loss. If possible a baseline hearing and balance tests should be obtained. In the future, genetic screening may be available for the most common mutations responsible for drug induced hearing loss, especially with a positive family history. During treatment, monitoring of serum drug levels, kidney and liver function, and auditory or vestibular function should be performed. Ototoxic medications

should be avoided if there is a satisfactory alternative. The fluoroquinolones (e.g. ciprofloxacin) or broad-spectrum cephalosporins, for example, have largely replaced the need for aminoglycosides as a first line antibiotic. Also it is important to avoid use of different ototoxic medications at the same time, such as co-administration of loop diuretics and aminoglycosides or combining vancomycin and an aminoglycoside.

The purpose of auditory monitoring is the early detection of hearing loss that might develop during treatment before it becomes clinically significant. A baseline test series should be obtained before treatment, provided that this testing does not significantly delay critical antibiotic treatment. These tests could include pure tone audiometry and word recognition, high frequency audiometry above the standard 8000 kilohertz high tone limit, and otoacoustic emissions, if available. Recommended protocols for audiological monitoring for platinum-based chemotherapy include testing prior to each cycle and for 1-2 years after treatment. For aminoglycosides, testing should be every 1-2 weeks, and 6 months after treatment.[51]

Detection of the development of unsteadiness or a bobbing visual field, known as oscillopsia, is important and should alert the health care worker that vestibular damage may be present. Although there is no specific protocol for vestibular monitoring, clinical tests such as the dynamic visual acuity, post-head shake nystagmus, and high-frequency head thrust may help to detect vestibular losses earlier. Standard laboratory tests include electronystagmography or videonystagmography, slow or high frequency rotation tests, and computed dynamic posturography. A description of these tests is beyond the scope of this chapter and these tests may be difficult in very young patients.

An Intriguing prospect for the future is the possibility of protective therapy when ototoxic medications are used. The goal of such therapy would be to prevent ototoxicity, while not reducing the effectiveness of medications. The utility of co-administration of aspirin in an adult population has already been demonstrated, but the dose and safety of this therapy for children has yet to be evaluated.[22] Protective substances could be given systemically, as in the case of aspirin, or intratympanically. The intratympanic route might allow round window absorption of the protective substance into the inner ear while not interfering with the desired medication effect systemically. In addition to salicylates a partial list of substances that may lessen the ototoxic effect of aminoglycosides include anti-oxidants, such as iron-chelating agents, superoxide dismutase, transforming growth factor alpha, and inhibitors of cell death pathways such as c-Jun N-Terminal kinase inhibitory peptide and caspase inhibitors. For cisplatin or carboplatin, there are thiol compounds, anti-oxidants, and inhibitors of cell death pathways.

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