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Ototoxicity in dogs and cats

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Synopsis

A variety of drugs in veterinary use have side effects that can potentially damage the senses of hearing or balance in animals. A large body of literature exists on the incidence and mechanisms of “ototoxicity” in experimental animals and in humans, but little is documented in domestic dogs and cats. However, the generality of these adverse actions across species allows us to extrapolate and provide the veterinarian with insight into possible complications of chemotherapy.

Keywords

hearing loss; cisplatin; aminoglycosides; diuretics

Introduction

The awareness that therapeutic treatments sometimes impose undesirable side effects ranging from minor inconveniences to death is probably as ancient as the practice itself of treating ailments with herbs and drugs. In particular, the knowledge that some agents have the potential to adversely affect our senses of hearing and balance has a history going back at least a thousand years.¹ It is notable that these side effects were all first discovered in humans, including the landmark discoveries of auditory and vestibular toxicity (ototoxicity) of aminoglycoside antibiotics and cisplatin in the 20th century. Only subsequently did laboratory experiments establish animal models from which further insight into toxic mechanisms was gained and which can be used to delineate safe or protective treatments.

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A surprisingly wide variety of drugs are potentially ototoxic, varying in chemical structure and therapeutic targets (Table 1). In human medicine, the list includes drugs of past interest (e.g. arsenicals, mercurials), drugs that only cause a temporary effect on hearing (e.g., salicylates), and drugs in current use associated with a significant incidence of permanent hearing loss (aminoglycosides, cisplatin). Of potential concern in veterinary practice are primarily the antibacterial aminoglycoside antibiotics gentamicin and amikacin, the anti-cancer agent cisplatin, and loop diuretics like furosemide, all of which will be discussed in this article. Some ototoxic potential might also be associated with occasionally or rarely used drugs such as the anthelmintic arsenical melarsomine and the antibiotic erythromycin. It is of interest to note that some of these therapeutics also exhibit renal toxicity, as has been documented for aminoglycosides and cisplatin, as well as some non-steroidal anti-inflammatory agents. Finally, in considering potential causes of hearing loss in animals, environmental factors should not be overlooked, such as advanced age and even exposure to noise in large kennels.²

Ototoxicity in dogs and cats

The incidence of therapy-linked ototoxicity in domestic dogs and cats is difficult, perhaps impossible, to establish. Subtle changes in hearing will go largely unnoticed by pet owners because these animals either will rely more on or compensate with their other senses. Verbal commands are frequently accompanied by body language that helps their interpretation in the presence of a compromised hearing, and visual cues and some inherent plasticity of the vestibular system will hide small effects on balance. As a result, animals with auditory or vestibular deficits may function reasonably well in a familiar environment, an adaptation that is likewise observed in humans. However, with increasing duration of chemotherapy as might be needed for cancer or with confounding factors such as aging the impediments can become so severe as to affect gait and balance or even be a risk to life if an approaching danger such as a car cannot be heard. This article will address the potential ototoxicity of cisplatin, gentamicin, furosemide, and related compounds, drawing from laboratory animal studies and human clinical trials, which have been well documented over decades of research and experience.

Gentamicin

Gentamicin is one of the aminoglycosides, a class of antibiotics which is effective mainly against gram-negative bacteria. Since the discovery of the first aminoglycoside (streptomycin) in 1944³ and, subsequently, other compounds of this class (gentamicin in 1963)⁴, they have been widely popular due to their broad antibacterial spectrum, non-allergenic characteristics, and inexpensive cost. In cats and dogs these drugs are primarily used to treat septicemia and infections of bone, joints, the respiratory tract, skin, soft tissue, urinary tract, and uterus, and are given topically for ear infections. Aminoglycosides generally are administered systemically (intravenously, intramuscularly, or subcutaneously) or topically into the ear, and all routes of administration have the potential to lead to ototoxic side effects. They are ineffective given orally as they are not absorbed enterically.

Although the antibacterial action is rather complex, a major contributing mechanism appears to be an inhibition of protein synthesis accomplished through binding to the bacterial 30S small ribosomal subunit.⁵ Due to their long history as therapeutics and sometimes uncontrolled use, bacterial resistance to aminoglycosides has been developing worldwide, not only in human hosts, but also in their veterinary applications.⁶ Nevertheless, they still serve as potent antibacterial agents and their judicious use can minimize the further development of resistance.

Incidence of ototoxicity

Because bacterial ribosomes, the therapeutic targets of aminoglycosides, differ structurally from mammalian ones, the drug action is largely specific for prokaryotes. However, mammalian mitochondrial RNA contains similar subunits and may represent a potential target for aminoglycoside antibiotics. In humans, mitochondrial mutations are a well-defined high risk factor in aminoglycoside-induced hearing loss.⁷ To the best of our knowledge, no such risk factors have been identified in domestic animals.

The pattern of ototoxicity differs between the various aminoglycosides, involving either the auditory system (cochleotoxicity) or vestibular system (vestibulotoxicity), or both, but across the board the deficits are typically bilateral, progressive, and essentially inevitable with long-term administration. Gentamicin targets both senses, often with a predilection for balance; amikacin, in contrast, may preferentially target the cochlea.⁸ Although a large body of information on ototoxicity in animals exists, the incidence of drug-induced hearing loss cannot be deduced because the goal of laboratory studies is to achieve ototoxicity with high-dose regimens in order to investigate mechanisms of cell death or prevention. In clinical studies, the reported incidence varies due to differing treatment regimens and, chiefly, varying assessment parameters and definitions of hearing loss. The estimated incidence of ototoxicity in humans, including both cochleotoxicity and vestibulotoxicity, ranges from 15–50%^{9–11} but such data include all measurable hearing and balance deficits and are not indicative of disabling conditions. Aminoglycosides may also cause nephrotoxicity, but there is no statistically significant relationship to ototoxicity and the incidence of co-occurrence is only 4.5%.¹²

Observation of cats in veterinary treatment confirms the potential for ototoxicity in this species. When renal failure, a frequent side effect of aminoglycoside antibiotics, was diagnosed in cats receiving paromomycin for treatment of infectious enteritis the authors also noticed deafness in three of those four cats.¹³ They attributed it to an “excessive dosage” of the drug confounded by renal failure. Apramycin, mostly used in livestock, was tested in a small number of dogs and cats as part of a toxicity assessment. Chronic oral administration to beagle dogs produced little or no signs of nephrotoxicity or ototoxicity probably because of poor absorption after oral dosing. Subcutaneous injections into cats (20% aqueous solution for 30 days) caused severe nephrotoxicity but a possible vestibular problem in only one of the four animals.¹⁴ Clearly, both the type of aminoglycoside and the route of administration can influence the nature and incidence of adverse side effects.

Of special concern is the fact that the aminoglycoside antibiotics can cross the placental barrier and, thus, have the potential to cause deafness in the fetus. Experimental studies in rats, mice, guinea pigs, and cats have confirmed the existence of a “critical period” in development when sensitivity to ototoxic agents is greatest.^{15–17} This critical period coincides with the development of the inner ear both in altricial and precocial mammals.¹⁸

Internal ear pathology

Although various types of cells in the internal ear are affected by long-term administration of aminoglycosides, the sensory cells, predominantly the outer hair cells (OHC) are the primary target of the drugs. These non-regenerative OHCs begin to die off in the basal region of the cochlear spiral and losses progress towards the middle and apical turns as the lesions worsen. This corresponds with the clinical and experimental observations of initial deterioration of hearing at higher frequencies, which are processed in the basal turn.¹⁹ Such a primary effect on high frequencies might be particularly disturbing for animals such as dogs that possess hearing at ultra-high tones. However, prolonged treatment or high doses of drugs will increasingly affect lower frequencies and impact the animals’ (and human)

communication range. Other structures in the internal ear are affected later, including the stria vascularis, the structure essential to maintain cochlear homeostasis, and the spiral ganglion cells of the nerve connection to the brain. Although loss of hair cells is the primary reason for the decline of hearing function, all of these pathological changes are contributing factors and have been observed in both cats and dogs^{20, 21}.

Aminoglycoside antibiotics are also able to produce vestibular lesions and consequent behavioral deficits. An impaired balance is similarly caused by loss of the sensory hair cells of the vestibule, primarily type I hair cells, followed by type II hair cells. The cells are first lost in the apex of the cristae ampullares, the structure responsible for the detection of angular acceleration and deceleration.²² Damage may also involve the striolar regions of the maculae in utricle and sacculus. Early studies attest to the fact that cats can be affected by the vestibular side effects of aminoglycosides^{23, 24} but these were laboratory experiments using high doses of the drugs. As mentioned before, such studies indicate the potential toxicity but cannot predict an incidence of vestibulotoxicity in a normal veterinary treatment.

Molecular mechanisms

Oxidative stress caused by the overproduction of reactive oxygen species (ROS) is implicated in aminoglycoside ototoxicity by many reports.^{25–27} ROS, or free radicals, are normal byproducts of metabolism and contained by the cells' complement of antioxidants. Their excessive formation, however, triggers several well-defined pathways of cell death in the affected cells, including caspase activation and the c-Jun NH2-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) pathway, as well as caspase-independent apoptotic and necrotic pathways.²⁸

Prevention of ototoxicity

The formation of ROS and subsequent cell death in the cochlea are successfully prevented by the co-administration of antioxidants or similar scavengers of ROS. The efficacy of such co-treatment has been well established in laboratory studies in several species where, for example, gentamicin-induced ototoxicity could be reduced both morphologically (prevention of hair cell loss) and functionally (attenuation of hearing impairment).²⁹ The list of beneficial antioxidants includes deferoxamine and dihydroxybenzoic acid (as iron chelators they prevent the "Fenton-Reaction" of ROS formation), glutathione, α -lipoic acid, D-methionine, N-acetylcysteine, herbal preparations (e.g., *Salviae miltiorrhizae* extract), and many more. A randomized double-blind placebo-controlled clinical trial extended the observation of therapeutic protection to patients receiving gentamicin for acute infection. Aspirin, given for its iron-chelating and antioxidant properties, significantly reduced the incidence of gentamicin-induced hearing loss, from 13% (14 of 106 patients) in the placebo group to only 3% (3/89) in the aspirin group.³⁰ These experimental and clinical results strongly support the notion that the formation of ROS causally relates to cell death pathways in aminoglycoside ototoxicity and that antioxidants are potent antidotes.

Despite such progress in prevention, there is presently no guideline for protective co-treatments for dogs and cats receiving potentially ototoxic medications. Since the effects of antioxidants on aminoglycoside ototoxicity have proven quite robust across species, antioxidant supplements might be interesting candidates for veterinary medicine because of their easy availability, safety, and low cost. Extrapolating from laboratory studies, antioxidant treatment might be most efficacious if the patient can be pretreated with the antioxidant as well as receive co-treatment for the duration of the aminoglycosides course. To this date, even experimental studies of prevention of ototoxicity in dogs and cats are lacking and it remains uncertain which antioxidants are effective in these species. Aspirin,

for example, would have to be ruled out because of its high toxicity to cats. It is very encouraging, however, that the antioxidants silymarin and vitamin E are effective against the renal side effects of gentamicin in dogs.³¹

Cisplatin

Since its introduction as an antineoplastic agent in the 1960s, cisplatin has been applied broadly to a variety of malignant tumors, including testicular, ovarian, bladder, and head and neck tumors in humans³² and is likewise used in veterinary medicine. An early and clinically significant adverse effect of cisplatin is nephrotoxicity, which can cause irreversible damage to the kidney. However, nephrotoxicity can be successfully reduced by adequate pre- and post-treatment hydration and concomitant diuresis. Avoidance of the other typical adverse effects of cisplatin, ototoxicity and neurotoxicity, does not have any clinically prescribed regimen or prevention yet, although recommendations are often made to dose slowly over days and weeks to avert toxicities.

The primary effect of cisplatin in cancer cells is to inhibit DNA replication by intercalating with the bases (binding preferably to the 7-nitrogen atom of guanine), and eventually induce cell death by apoptosis.³³ While cisplatin is generally highly effective, pathways of resistance do exist, including decreased cellular accumulation (reduced uptake), inactivation of cisplatin by glutathione and metallothionein, enzymatic DNA repair, and resistance to apoptosis.

Incidence of ototoxicity

The pathophysiological damage from cisplatin ototoxicity is mostly irreversible. The auditory system is affected almost exclusively and cisplatin-induced hearing loss, just like aminoglycoside-induced hearing loss, will commence at the high frequencies. The hearing loss is bilaterally progressive and profound. Its severity is cumulatively dose-dependent and may continue to progress after the administration of the drug is completed. In clinical situations, up to 100% of patients may sustain some degree of hearing loss with prolonged treatment.³⁴ Various species of experimental animals are likewise susceptible to this drug and the incidence of hearing loss generally is high.³⁵

Internal ear pathology

Although loss of OHCs is a major pathological feature, the action of cisplatin on the internal ear appears to be more complex than that of the aminoglycosides, affecting a variety of cell types. Along with hearing loss at higher frequencies, audiological findings in cisplatin ototoxicity include reduction of the endocochlear potential,³⁶ the electrochemical driving force generated by the stria vascularis and necessary for the transduction of the acoustic stimulus into receptor potentials and subsequent nerve impulses to the brain. Elevation of the thresholds for both the compound action potential^{37, 38} and the cochlear microphonic,^{38, 39} imply a compromised function of vestibulocochlear nerve fibers and outer hair cells (OHCs), respectively. Indeed, observations from both human temporal bones and experimental animals confirm pathological changes encompassing the organ of Corti, stria vascularis and spiral ganglion cells. On the other hand, the vestibular system is notably unaffected.³⁷

Molecular mechanisms

Just as is the case for aminoglycosides, the excessive production of reactive oxygen species (ROS) appears to be central to cisplatin ototoxicity,⁴⁰ and an internal ear-specific NADPH oxidase, NOX3, plays an important role in generating those ROS.⁴¹ ROS will then initiate a cascade of cell death pathways leading to apoptosis, where several caspases and Bcl-2

family proteins are activated.⁴² Success in experimentally ameliorating cisplatin-induced hearing loss by interfering with these signaling pathways supports a causal relationship between the molecular observations and auditory deficits. As a case in point, the inhibition of NOX3 in the rat cochlea led to the protection of the ear from cisplatin ototoxicity.^{43, 44} Likewise, inhibitors of caspases protected OHCs and preserved hearing function.⁴⁵ These results, however, are derived from laboratory studies that have not yet led to clinical application.

Prevention of ototoxicity

Given an ROS-based mechanism of cisplatin toxicity, antioxidants have been extensively explored as protective agents^{35, 46, 47}. Supplements tested for their efficacy include glutathione, superoxide dismutase, vitamin C, vitamin A, vitamin E, and transferrin. Here again, studies in animal models have had success^{47, 49} but clinical studies of antioxidant-based amelioration of cisplatin ototoxicity are minimal⁴⁸. Nevertheless, it is interesting to note that antioxidants are possibly the most commonly used supplements in cancer patients, thought to treat the cancer directly, as well as increase immune function and reduce toxicity of cancer chemotherapies. Of specific interest is the fact that antioxidants have been used in veterinary medicine as cancer therapy or adjunct with medications like cisplatin.^{50–52} This treatment is, however, not without caveat. It has been argued that reducing the toxicity with antioxidants may also reduce cisplatin efficacy towards cancer cells and, hence, efficacy of the chemotherapy. The topic is still controversial and under discussion.⁵³

Diuretics

Furosemide is one of the most commonly used loop diuretics, acting on epithelial cells in the loop of Henle of the kidney, and a drug of choice to treat edema and hypertension. Depending on the dose and the rate of the administration, furosemide can cause several side effects. Electrolytic abnormalities, such as hyponatremia and hypokalemia, as well as dehydration are common because furosemide changes the level of electrolytes in the blood and the body's total fluid volume. In addition, ototoxicity can be a side effect of furosemide that is, in contrast to aminoglycosides and cisplatin, mostly temporary and rarely permanent.^{54, 55} However, furosemide has the ability to potentiate cisplatin and aminoglycoside-induced hearing loss to the extent that combination treatment may lead to complete deafness even at individually safe doses of the two agents.^{56–59} This danger of potentiation is shared with other diuretics, for example, ethacrynic acid. The mechanism behind potentiation is unknown, but the diuretic may increase the concentration of the ototoxins in the cochlear endolymph.

Incidence of ototoxicity

Little is known about the clinical incidence of ototoxicity of diuretics since most cases of hearing impairment are transient. One study on humans reported that 4 of 62 (6.4%) of those receiving furosemide had at least a 15 dB elevation of pure tone auditory thresholds⁶⁰ and hearing losses were greatest in the middle frequencies. It can be expected that the adverse effects depend on the dose and the frequency of administration. Vertigo has only been seen as an infrequent side effect of furosemide therapy.

Internal ear pathology

The pathology induced by diuretics differs significantly from aminoglycosides and cisplatin (Table 2). Diuretics such as furosemide will primarily act on the non-sensory tissues of the internal ear and by mechanisms detectable only by invasive physiological measurements that elude routine examination in patients. One manifestation, for example, is a decreased endocochlear potential observed in several animal species, including the dog and the

cat.^{61, 62} Furosemide also reduced the amplitude of the vestibulocochlear nerve action potential in the cat and the dog.^{60, 63, 64} The cochlear microphonic is also affected.^{65, 66} Corresponding to those functional changes, edema in the stria vascularis and degeneration of intermediate cells of the stria vascularis were observed in guinea pigs.⁶⁷ The same kind of morphological change was reported in a study of a human temporal bone.⁶⁸ All of these changes are generally reversible and no permanent morphological damage to hair cells has been found.

As with aminoglycoside antibiotics, animals in their developmental period are more susceptible to furosemide. Young rat pups have significantly greater reductions in endocochlear potential after diuretic treatment and higher elevation of compound action potential thresholds than rats older than 30 days.⁶⁹ The observed physiologic changes were accompanied by edema of the stria vascularis. To what extent other animal species are susceptible has not yet been explored.

Molecular mechanisms

The molecular mechanism of ototoxicity of diuretics appears closely related to their pharmacological properties. Both the kidney and the internal ear have extensive ion-transporting epithelia that are targeted. Consistent with such a mechanism, treatment of guinea pigs with furosemide caused an increase in the sodium concentration and a reduction in potassium activity in the endolymph.⁷⁰ This effect may occur via a blockade of active potassium transport in the stria vascularis and is in accordance with the documented decrease of the endocochlear potential.

Prevention of ototoxicity

Due to the numerous distinctions between the pathologies of furosemide ototoxicity and that of cisplatin and aminoglycosides, antioxidant therapy cannot be assumed to be effective against furosemide ototoxicity. Several other agents, however, have been shown to attenuate the ototoxicity of diuretics; inhalation of oxygen, co-administration of triamterene (a potassium-sparing diuretic), iodinated benzoic acid derivatives (diatrizoate and probenecid) and organic acids (sodium salicylate and penicillin G) provided some protection.^{60, 71} Overall, however, pharmacological intervention is of little clinical concern because the ototoxicity of diuretics is usually transient.

Conclusion

- Although little direct data exist on the ototoxicity of drugs in cats and dogs, information from laboratory animals and human patients suggests that domestic animals are similarly susceptible to the major causative agents cisplatin, aminoglycosides and diuretics.
- Initial signs of aminoglycoside-induced hearing loss (gentamicin, amikacin) in dogs and cats are difficult to assess in daily life. Standard acoustic “startle tests” (clapping your hands behind an animal’s back) might be helpful, but are not very sensitive. Alternatively, signs of vestibular dysfunction such as vomiting, and disturbance of gait in severe lesions may be easier to detect.
- Initial indications of cisplatin-induced hearing loss may likewise not be apparent in daily activities. Signs of vestibular dysfunction are unlikely because of the drug’s preferential action on the auditory system. If initial audiologic deficits from cisplatin (or, for that matter, aminoglycosides) remain unnoticed and the drug continues to be administered, the animals can be expected to develop severe hearing loss.

- Administration of aminoglycosides to pregnant dogs or cats may lead to hearing deficits in their offspring.
- Because most cases of diuretic-induced ototoxicity are only transient, close attention to the dose and rate of injection may avert permanent damage to the inner ear.
- Newborn or older animals are at greater risk for ototoxicity.
- Combination of diuretics with aminoglycoside antibiotics or cisplatin will, in experimental animals and in humans, potentiate for profound, permanent hearing loss.
- It is possible that ototoxicity in general can be averted by monitoring of hearing and balance and early cessation of treatment or substitution of different drugs.
- Supplementation of various antioxidants has been demonstrated to attenuate ototoxicity induced by aminoglycosides and, to some extent, cisplatin. Guidelines for palliative treatment of cats and dogs is not yet available.

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Glossary

This glossary will not provide complete anatomical or physiological information but is intended to convey the meaning or interpretation of technical terms. Additional information can be found in other articles in this issue.

Auditory thresholds	The lowest sound intensity that evokes a "hearing" sensation. In animals it is generally measured by auditory brain stem evoked responses which are recorded non-invasively as a train of electrical waves that travel along the auditory pathway. Auditory thresholds obtained in this fashion are an objective and sensitive determinant of hearing acuity or hearing loss
Cochlear microphonic	A sound-evoked electrical potential that originates in the outer hair cells and can be taken as an indicator of their proper function
Compound action potential	It reflects the activity of hair cells and the action potentials of the auditory afferent nerves and thereby provides information on the normal or abnormal processing of sound in the cochlea
Cristae ampullares, sacculus, utricle	These are individual structures of the vestibular system that adjust our balance to angular or linear acceleration and gravitational pull. The macula is the sensory part of the sacculus and the utricle, containing hair cells; the striola is a central segment of the macula
Endocochlear potential	The large positive potential in the endolymph fluid created by its ionic composition. Changes in the endocochlear potential (usually a decrease) will impair the transduction process and increase auditory thresholds
Endolymph	One of the two fluids in the cochlear duct, the other one being perilymph. It has a unique ionic composition among extracellular body fluids (low Na ⁺ , high K ⁺) which helps create the electrical

	gradient that drives the transduction process, the conversion of sound into nerve impulses
Hair cells	The general term for the sensory cells in the cochlea and the vestibular system that carry out the transduction process, the conversion of sound into nerve impulses. Several types of hair cells can be morphologically and functionally distinguished. Inner hair cells are the primary transducers of sound in the cochlea; outer hair cells enhance transduction in the cochlea; type I and type II hair cells are part of the vestibular sensory apparatus
Organ of Corti	The structure in the cochlea that houses the sensory cells (hair cells) and additional so-called supporting cells
Spiral ganglion	The section of the cochlear nerve that directly innervates the hair cells
Stria vascularis	A supporting structure in the cochlea. Its ion transport mechanisms create the ionic environment and electric potential of the endolymph

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Key Points

- Aminoglycosides (e.g., gentamicin, amikacin) and cisplatin are the drugs of highest concern for ototoxicity
- Loss of sensory cells (hair cells) in the internal ear is the primary cause of permanent deficits in hearing or balance.
- Use of compensatory mechanisms by domestic animals (observation of body language with spoken commands or visual cues to aid balance) may obscure or delay the detection of sensory deficits.

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Table 1**POTENTIAL CAUSES OF HEARING LOSS**

Aminoglycoside Antibiotics	Streptomycin, neomycin, gentamicin
Antineoplastics	Cisplatin, carboplatin
Diuretics	Ethacrynic acid, furosemide
Metallo Compounds:	Arsenical, mercurials
Antimalarial	Quinine
Analgesics, Antipyretics	Salicylates
Polypeptide Antibiotics	Viomycin, vancomycin
Macrolide Antibiotics	Erythromycin
Industrial Solvents	Toluene, organotins
Environment	Noise, age

The table lists representatives of potentially ototoxic agents and environmental causes of hearing loss. Information is derived from literature on experimental animals and clinical data.⁸ The compilation is intended to show the range of drugs and environmental factors that can affect the auditory (and to some extent the vestibular) system in mammals. As further outlined in the text and in Table 2 the effects of the various agents may be transient or permanent and the incidence of such effects can be highly variable.

Table 2**EFFECTS OF OTOTOXINS ON THE INTERNAL EAR**

	Aminoglycosides	Cisplatin	Furosemide
Type of Hearing Loss	Usually permanent	Usually permanent	Usually temporary
Frequency Range of Hearing Loss	High frequencies with progression to lower frequencies	High frequencies with progression to lower frequencies	Middle frequencies
Hair Cell Loss	Beginning in the base and progressing toward the apex	Beginning in the base and progressing toward the apex	None
Changes in the Stria Vascularis	Gross degeneration only at later stages of intoxication	Generally observed; mostly in intermediate cells	Temporary effects on intermediate cells and stria edema
Changes in the Cochlear Nerve	Nerve degeneration following hair cell loss	Damage at the basal coil, and decrease in function	Temporary impairment of function
Side Effects on Balance	Possibly severe with some but not all aminoglycosides	Not expected	Not expected