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DRUG OTOTOXICITY

Leonard P. Rybak

Departments of Surgery (Otolaryngololgy) and Pharmacology, Southern Illinois University, School of Medicine, Springfield, Illinois 62708

INTRODUCTION

Ototoxicity may be defined as the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, and especially of the end organs and neurons of the cochlear and vestibular divisions of the VIIIth cranial nerve (1). This is in contrast to neurotoxic drugs that may affect hearing or equilibrium by acting primarily on the brain-stem nuclei and central auditory or vestibular connections. Drug-induced hearing loss is one of several potential causes of iatrogenic deafness. The dangers of ototoxic agents such as quinine, arsenic, alcohol, aniline, and oil of chenopodium have long been recognized (2). Ototoxic agents in current clinical use include the aminoglycoside antibiotics, loop diuretics, nonsteroidal anti-inflammatory agents, chemotherapeutic agents and a variety of miscellaneous drugs. This review is limited to therapeutic agents most likely to cause hearing loss in humans.

ANATOMY AND PHYSIOLOGY OF THE AUDITORY PERIPHERY

The temporal bone is one of the complex bones of the cranial base. It contains the external auditory canal, tympanic membrane, middle and inner ear, vestibular apparatus, and the cochleovestibular and facial nerves. The inner ear or cochlea is a hollow, spirally wound tube, resembling a snail shell, which houses the auditory end organ. The cochlea is filled with fluids of distinct composition, endolymph and perilymph. The endolymph is contained within the central compartment or scala media, which also contains the basilar membrane and the organ of Corti, where the sensory cells (inner and outer hair cells) are suspended by supporting cells. The organ of Corti includes one row of inner hair cells and

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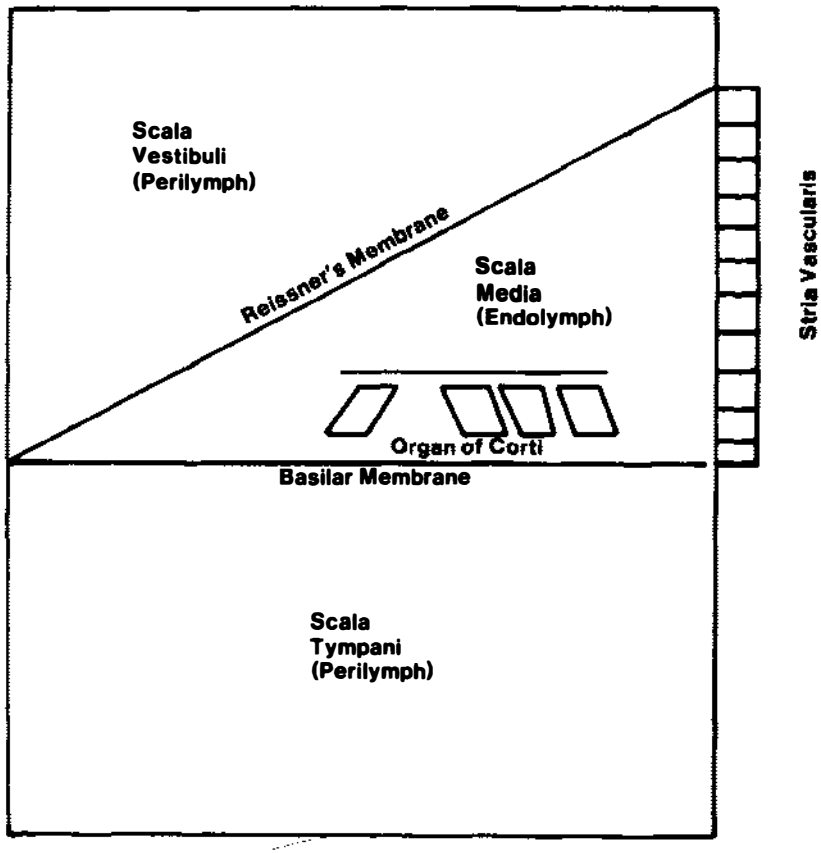

Figure 1 Schematic cross-sectional diagram of the cochlea.

three rows of outer hair cells; the supporting cells; the tunnel of Corti [a triangular space between the inner and outer hair cells (Figure 1)]; both efferent and afferent nerve endings; and the basilar and tectorial membranes. The primary auditory afferent dendrites convey impulses from the hair cell–eighth nerve synapse to the cell body in the medial wall—the spiral ganglion. The axons of the spiral ganglion leave the temporal bone via the internal auditory canal and travel intracranially to synapse in higher auditory centers in the brain stem. Space does not permit a complete description of current concepts of the physiology of hearing. The reader is referred to several recent publications for review (3–6).

Since its discovery in 1950, the resting endocochlear direct current (dc) potential (EP) has been studied by a number of investigators. The EP appears to consist of two components: a positive portion thought to be produced by an electrogenic sodium potassium pump, which can be inhibited by anoxia or

ouabain; and a negative component unmasked by inhibitors such as anoxia or loop diuretics. The negative component is thought to result from potassium diffusion or a leakage of current from the cells of the organ of Corti (4). Fluid in the central compartment of the cochlea, endolymph, is very high in potassium but low in sodium content. On the other hand, perilymph (in the scala vestibuli and the scala tympani) is high in sodium and low in potassium. Perilymph is similar to the fluid that bathes the lateral surface of the receptor cells in the organ of Corti—the so-called cortilymph. Compartmental analysis strongly suggests that perilymph is an ultrafiltrate of plasma and that perilymph is the precursor of endolymph (7, 8).

The most thoroughly investigated sound-dependent potential is the cochlear microphonic (CM) potential. It can be recorded from various locations in and near the inner ear or even from the scalp. An electrode connecting the round window of an experimental animal to a suitable amplifier and loudspeaker will reproduce the voice of an individual who speaks into the ear of the animal. This potential most likely originates from the hair cells, and the recordings obtained from the round window reflect the activity of mainly the outer hair cells in the base of the cochlea. The summating potentials (SP) are dc potentials that can be most effectively recorded from the scala media inside the cochlea in response to a continuous tone. SP may consist of several components originating from different sources, such as the outer hair cells (+SP) and inner hair cells (−SP) (4).

The compound action potential (CAP or AP) is a sound-dependent potential reflecting excitation and synchronization of populations of auditory nerve fibers (3). The response is most prominent following transient stimuli such as clicks and the potential is composed of two negative peaks, named N_1 and N_2. The magnitude of the N_1 response is a function of both the stimulus intensity and the number of fibers firing synchronously. The N_1 amplitude and latency are thought to reflect the integrity of the cochlea and eighth nerve, whereas the N_2 component may originate from more central structures.

The auditory brain-stem response consists of a series of waves that can be recorded from the scalp. They may represent sequential activation of the auditory neuraxis in the brain stem. Single auditory nerve fibers can be studied with a microelectrode inserted into the nerve by an intracranial approach. These cells can be characterized by their spontaneous rate and pattern of firing and by the rate and pattern of firing with stimuli of known frequency and intensity. Both the receptor cells of the cochlea (inner hair cells) and the single neurons of the spiral ganglia and eighth nerve exhibit exquisite frequency selectivity, as demonstrated by the tuning curve. The tuning curve is a plot of neuron firing above threshold at various frequencies. The neural response at various frequencies is not the same, as one can see readily from the plot of the tuning curve. A turning curve consists of a low-frequency tail portion that indicates

hearing response only to high-intensity sounds, and an extremely sharply tuned "tip" region. The latter is characterized by an extremely sudden transition from the high-threshold tail region to a narrow region where the nerves or receptor cells respond to their characteristic frequency. In this area, the neuron or receptor cell increases its firing rate abruptly at tones of low intensity near the characteristic frequency. At frequencies above the characteristic frequency, there is again an abrupt and rapid rise in the threshold of the neuron (3, 4). Auditory neurons also exhibit activity in the absence of sound (spontaneous activity) (4).

Spontaneous otoacoustic emissions and stimulated emissions (cochlear echoes) are interesting phenomena demonstrating that the reverse transmission of acoustic energy is in the cochlear partition. These may be generated by the so-called cochlear amplifier that may reside in the outer hair cells (5, 6).

Transduction of sound energy into electrical impulses transmitted to the brain is a complex process about which much is unknown. The shearing of the stereocilia of the hair cells relative to the tectorial membrane appears to elicit a receptor potential in the inner and outer hair cells. This presumably triggers the release of the excitatory afferent neurotransmitter that has not yet been fully characterized. Polyphosphoinositides, which appear to play a significant role in transduction in a variety of mammalian tissue cells (9), have been implicated in cochlear transduction recently (10) and may play a role in the ototoxicity of aminoglycosides.

OTOTOXIC ANTIBIOTICS

Aminoglycosides

The aminoglycoside antibiotics are a class of broad-spectrum antibiotics active against gram-positive and gram-negative organisms as well as mycobacteria. A large number of aminoglycoside antibiotics are in clinical use. Detailed descriptions of the chemistry and structure-activity relationships of aminoglycosides are available. The vestibulotoxic compounds such as streptomycin, gentamicin, and tobramycin tend to selectively destroy type I hair cells of the crista ampullaris (1). The cochleotoxic agents such as neomycin, kanamycin, amikacin, sisomycin, and lividomycin appear to cause a pattern of injury to the cochlea in experimental animals given ototoxic doses of these drugs similar to the injury pattern seen in human temporal bone studies (11).

Some comparative studies have been performed to rank aminoglycosides in order of their probability of auditory toxicity. Animal (12, 13) and clinical (14) studies suggest that netilmicin and dibekacin (15) may be considerably less ototoxic than other aminoglycosides currently in widespread use such as gentamicin, tobramycin, kanamycin, and amikacin. Comparisons of ototoxicity with antibacterial activity have shown that netilmicin has the highest therapeutic

index. Tobramycin has been ranked next, followed by gentamicin C. Amikacin is said to have a therapeutic ratio less than 10% of netilmicin and 50% of that of tobramycin (16). Clinical studies show that the average incidence of cochlear toxicity was 13.9% for amikacin, 8.3% for gentamicin, 6.1% for tobramycin, and 2.4% for netilmicin (17).

MORPHOLOGIC CHANGES The earliest cochlear lesions produced by aminoglycoside antibiotics in experimental animals and humans appear in the outer hair cells of the basal turn. The initial ultrastructural findings are fusion of stereocilia to form giant hairs (18). As the dosage and duration of administration of antibiotic is increased, the lesion extends apically, then to the inner hair cells (1, 19). The pattern of inner hair cell destruction varies, and may parallel or occur in the gradient opposite to that of the outer hair cells. This raises questions about the selectivity of aminoglycosides for the destruction of outer hair cells (20). Delayed degeneration of the afferent nerve endings after cessation of treatment can follow destruction of the inner hair cells (21). Damage to other cochlear structures lining the cochlear duct (including the spiral ligament, stria vascularis, vestibular membrane, spiral prominence, and pericapillary tissues of the outer sulcus) was described in animals treated with kanamycin (1). Hair cell damage and auditory dysfunction may be asymmetrical (11, 22).

PHARMACOKINETIC STUDIES Because of the ease of obtaining pure samples, most studies of aminoglycoside pharmacokinetics have looked at the relationship of drug concentration in perilymph over time compared to simultaneous plasma concentration. It has been postulated that the slower rate of elimination of aminoglycosides from perilymph compared to plasma may be related to the aminoglycosides' cochleovestibular toxicity. Neomycin has the slowest elimination from the perilymph and also was the most ototoxic (23). Although earlier studies had suggested accumulation of aminoglycoside antibiotics in the perilymph of animals given large parenteral doses of aminoglycoside, gentamicin does not appear to accumulate in the perilymphatic compartment. Following prolonged infusion in animals, the perilymph-to-plasma ratios remained within a narrow range regardless of the plasma levels (24). This relatively constant ratio did not support the hypothesis of unlimited accumulation of aminoglycoside antibiotics in inner ear fluids, nor did it confirm the hypothesis of a "threshold" for entry into perilymph suggested by previous investigators (25). A review of the literature on the pharmacokinetics of aminoglycoside antibiotics in animals concluded that the vast majority of studies looked at concentrations of drugs in perilymph rather than endolymph, that their peak concentration in perilymph is reached later than the plasma peak, and that the half-lives of aminoglycoside in perilymph varied from 8 to 15 hours, which was much longer than the corresponding half-life in plasma (26).

Because of technical difficulties in obtaining pure endolymph, very few studies have been conducted on this fluid. Gentamicin enters this deep compartment extremely slowly. Following a constant infusion of gentamicin, the mean concentration of gentamicin achieved in endolymph by the end of the second day equaled that observed in a previous study after six days. This suggests that surrounding tissues have a large capacity to bind aminoglycosides or that a transport mechanism of the drug toward the endolymph became saturated (27).

PHYSIOLOGIC EFFECTS Physiologic consequences of such damage include the shift and attenuation of the input-output (sound intensity versus amplitude of response) curves for the AP and CM. The resulting shifts in CM and N_1 thresholds have been observed, as well as elevation of threshold of single auditory fibers in the high-frequency range. Tuning curve tips appear to be blunted with hypersensitivity of the tails (21, 28) and a decreased rate of spontaneous activity (29).

POSSIBLE MECHANISMS OF OTOTOXICITY Hypotheses have been proposed attempting to relate renal tubular transport of aminoglycosides to their nephrotoxic and ototoxic mechanisms. Aminoglycoside ototoxicity was originally thought to be caused by inhibition of protein synthesis in the organ of Corti (1). Although aminoglycosides can inhibit protein synthesis in mammalian liver mitochondria (30), this does not appear to be the mechanism for specific cellular destruction of the outer hair cells (31). It has been proposed that the aminoglycosides may inhibit carbohydrate uptake and/or metabolism and energy utilization in the outer hair cell. Kanamycin suppresses respiratory enzyme activity in the outer hair cell, with more pronounced effects on the basal turn (32). Biochemical studies suggest a selective inhibition of the Embden-Meyerhof pathway in the organ of Corti and in the kidney without alteration of the hexose monophosphate shunt (33). Neither pathway was found to be altered in the stria vascularis (33). This interference with carbohydrate metabolism may lead to inhibition of ATPase in the organ of Corti. There are reportedly fewer glycogen granules in normal outer hair cells of the basal turn of the cochlea, which is the area most susceptible to aminoglycoside damage, and these granules are depleted from the outer hair cells of animals treated with aminoglycosides (34). It has also been postulated that aminoglycosides may decrease the transport of glucose into the cochlea. Alloxan-diabetic rats were reportedly protected from kanamycin ototoxicity in proportion to the extent of hyperglycemia (35). The above concepts have been refuted by recent studies showing that gentamicin ototoxicity is not related to an effect on glucose uptake or utilization (36). On the other hand, diabetic rats were found to be protected from gentamicin-induced acute renal failure (37).

Phospholipids have been suggested as "receptors" for aminoglycoside anti-

biotic toxicity in both the membranes of the kidney and the inner ear (38). A series of experiments have led to the theory that ototoxicity caused by aminoglycoside antibiotics is related to phospholipid metabolism. Fractions of inner ear and kidney tissues each demonstrated high affinity for neomycin immobilized on glass beads (39). The components with this tendency to bind neomycin were two phospholipid fractions; namely, phosphatidylinositol phosphate and phosphatidylinositol diphosphate (39). Guinea pigs chronically treated with neomycin were found to have reduced labeling of phosphatidylinositol diphosphate in inner ear tissues when they were injected with radioactive phosphorus as a tracer to measure synthesis of these lipids (40). There appears to be a good correlation between effects of aminoglycoside drugs on cochlear microphonics and their interaction with polyphosphoinositide films in vitro (38, 41).

Some interesting recent studies of the lateral line organ of *Xenopus laevis* may explain all the biochemical findings discussed above and the clinical observations that, occasionally, the aminoglycoside antibiotics have reversible ototoxicity. Low concentrations of aminoglycoside antibiotics appear to have dual actions on sensory hair cells in the lateral line organ. The aminoglycosides appear to increase the spontaneous afferent nerve activity by altering the hair cell membrane. In addition, they markedly impair the mechano-electrical transduction process, perhaps by interfering with the motility of the sensory hairs (42). The gentamicin-induced loss of CM is reversed in the guinea pig with local perfusion of calcium (43). This also supports a two-step hypothesis for aminoglycoside ototoxicity: an initial membrane effect on phospholipids, antagonized by calcium; and a second step that is noncompetitive and leads to destruction of the hair cell. This hypothesis was further confirmed by double labeling experiments in which gentamicin was locally perfused into the ear and lipids were labeled by radioactive phosphate and radioactive glycerol. Uptake of radioactive phosphate into phospholipids was reduced in the organ of Corti, but labeled glycerol uptake into lipids was not altered in the ear treated with gentamicin. At the time that these effects were taking place, the CM were reduced but the ultrastructure of cochlear tissues was not altered. This may represent the reversible step that can be antagonized by calcium (43).

The aminoglycoside receptor in the cochlea may be a membrane-bound enzyme. Specific inhibition of proximal-tubule brush-border membrane phosphatidyl-specific phospholipase C in the kidney has been demonstrated (44). The binding of aminoglycosides to anionic phospholipids in the proximal-tubule cell membrane appears to be due to a charge interaction. This may allow sufficient aminoglycoside to enter the cell to allow an interaction with the above enzyme. By analogy, the receptor for aminoglycosides in the cochlea may be intracellular. Whether a similar enzyme exists in the cochlea needs to be explored.

Another explanation for the two-step hypothesis was briefly alluded to earlier. The initial step may be a charge interaction between the aminoglycoside and anionic phospholipids in the membrane of cells damaged by aminoglycosides. This interaction can be reversed by calcium. The second step may involve the inhibition of an important enzyme, such as phosphatidylinositol-specific phospholipase C, since the latter interaction is not altered by calcium in studies of the renal enzyme.

An alternative hypothesis was recently proposed to explain aminoglycoside ototoxicity, based on the finding that a radioprotectant compound WR 2721 [(3-aminopropylamino) ethyl phosphorothioate], which is thought to scavenge free radicals, protected guinea pigs against kanamycin ototoxicity as measured by behavioral and electrophysiological techniques (45). The onset of ototoxicity was delayed, its severity diminished, and its extent attenuated by pretreatment of animals with the radioprotectant compound. It was postulated that the mechanism of protection is mediated by scavenging of certain reactive species that may be generated by kanamycin in cochlear tissue (45). Another potential target for aminoglycoside ototoxicity is the protein melanin, suggested by the finding that albinos may be less vulnerable to aminoglycoside ototoxicity than are pigmented animals (46). Concomitant treatment of rats with fosfomycin appears to reduce both renal and inner ear damage caused by otherwise nephrotoxic and ototoxic doses of dibekacin (47). The mechanisms of this protective effect are unclear, but a chemical reaction between fosfomycin and dibekacin should be excluded.

Azthreonam is a new, completely synthetic monocyclic beta-lactam antibiotic that is active against aerobic gram-negative organisms and highly resistant to beta-lactamases (48). It is anticipated that azthreonam may replace aminoglycoside therapy in some patients. Preliminary studies show no evidence of ototoxicity in experimental animals (49).

Vancomycin

Vancomycin is a high-molecular-weight glycopeptide antibiotic that is structurally distinct from other currently used antibiotics. Recent advances in analytical techniques have permitted the complete elucidation of the structure of this unique antibiotic (50). Vancomycin and ristocetin are structurally related antibiotics that are both nephrotoxic and ototoxic and cause systemic reactions as well (51). The recent emergence of infections with methicillin-resistant strains of *Staphylococcus aureus* has resulted in a renewed interest in the use of vancomycin for such infections (52). Vancomycin is also used for enterococcal endocarditis in penicillin-sensitive individuals and is used orally for *Clostridium difficile* pseudomembranous colitis. Since some methicillin-resistant staphylococcal infections have failed to respond to vancomycin, rifampin or aminoglycosides may be added to the treatment regimen. An increased in-

cidence of nephrotoxicity in humans and animals receiving vancomycin and aminoglycosides has been observed (53), suggesting the possibility of increased ototoxicity as well. Hearing loss in humans has been reported at blood levels exceeding 45 mg/liter (54) but has also been reported at blood levels of 30 mg/liter or lower (55, 56). Initial symptoms of cochlear damage may include tinnitus or deafness. Reversible tinnitus has been correlated to "peak" serum levels of 40–50 mg/liter (57). The risk of vancomycin ototoxicity appears to be greater in persons older than 65 years of age, in patients receiving other potentially ototoxic drugs, and in patients with reduced kidney function. A recent study has documented the reduced total systemic and renal clearances of vancomycin in the elderly even with normal renal function (58). Vancomycin pharmacokinetics have been more completely characterized with the modern techniques of high-pressure liquid chromatography (59) and radioimmunoassay (58, 60). Multicompartmental models have been proposed (58, 61). It is therefore important to know from which phase of the pharmacokinetic curve one is sampling before any meaningful statements can be made relating blood levels and ototoxicity (61). Also, infusion rate can drastically alter "peak" concentrations (61). Vancomycin has a significantly longer half-life and volume of distribution in premature than in full-term infants. For this reason, careful monitoring of vancomycin blood levels in premature infants has been strongly recommended (60). Significant oral absorption does not usually occur after oral administration of vancomycin (62).

Erythromycin

Initial animal testing for possible adverse effects of erythromycin on the inner ear consisted of vestibular screening. It was concluded that no eighth nerve cranial damage could be attributed to erythromycin (63). However, the importance of erythromycin in treating pneumonias caused by *Legionella pneumophila* and related pathogens has probably resulted in the increased utilization of intravenous erythromycin. At least 32 cases of bilateral, sensorineural hearing loss, which is typically uniform across frequencies, have been reported in association with high doses of intravenously or even orally administered erythromycin (64). Patients most likely to experience hearing loss are elderly females with hepatic or renal failure or Legionnaire's disease who receive 2 g or more of erythromycin daily (65). Symptoms include decreased hearing, "blowing" tinnitus, and occasionally, vertigo. Although none of 30 elderly patients receiving large doses of erythromycin stearate had any change in hearing despite renal or hepatic failure (66), the half-life of erythromycin is prolonged in patients with renal failure, and the serum levels may be three to five times as high as one would predict in a patient with normal renal function (67). Ototoxic blood levels were measured in two patients; one patient's level ranged from 63 to 78 mg/liter (68) and the other had a serum level of 100

mg/liter (67). Auditory changes observed after erythromycin have been shown to be reversible following cessation of therapy. Animal experiments are needed to define more clearly the mechanisms of erythromycin ototoxicity.

Chloramphenicol

Ototoxicity experiences related to chloramphenicol have been restricted to patients receiving extremely high doses (69). Animal studies have shown damage to the cochlea following topical application of chloramphenicol resulting in loss of succinic dehydrogenase activity in outer hair cells and nerve endings (70). A recent study has shown that combined otitis media, noise exposure, and chloramphenicol produced enhanced cochlear damage in rats (71). On the other hand, ethacrynic acid was found not to potentiate the ototoxicity of chloramphenicol, in contrast to the marked potentiation of kanamycin ototoxicity by ethacrynic acid (72).

LOOP DIURETICS

The "loop" or high-ceiling diuretics include a series of compounds that are very potent inhibitors of ion reabsorption in the loop of Henle. These compounds include ethacrynic acid, furosemide, bumetanide, piretanide, azosemide, ozolinone, and indacrinone (73). The last two of these compounds have optical isomers. The (−) isomer of ozolinone has diuretic activity (74) and is ototoxic (75); (−) indacrinone is more potent than its (+) isomer (76). Each of the active loop diuretics has been found to affect cochlear function adversely in experimental animals and most of them have been shown to be ototoxic in humans (usually reversible). The exact incidence of hearing loss associated with loop diuretics is unknown. Two patients of a series of 283 (0.7%) developed deafness while taking ethacrynic acid (77). Significant audiometric changes were found in 1.1% of patients treated with bumetanide, whereas 6.4% of patients receiving furosemide were found to have hearing loss (78). More detailed reviews of clinical ototoxicity of furosemide are discussed in recent publications (79, 80).

Morphological Studies

Morphological studies of loop diuretics ototoxicity have been reviewed in detail (1, 81, 82). Morphologic changes in the cochlea associated with loop diuretics occur in the stria vascularis, while sensory structures appear to be little affected except by large doses of ethacrynic acid (81), which appears to be more cytotoxic to outer hair cells of the basal turn of the cochlea. Animals (82) and humans (83) receiving ototoxic doses of loop diuretics were found to have edema, both between and within cells of the stria vascularis and most markedly

in the basal turn. No changes were observed in the cochlear nerve fibers or ganglion cells.

Functional Changes

The EP is reduced in a dose-dependent manner by ethacrynic acid (19, 81), furosemide (84–86), bumetanide (87), and piretanide (88). Such changes are reversible, but the rate of recovery seems to be slowest for ethacrynic acid (89). The recovery of EP following furosemide injection correlates well with restoration of normal strial ultrastructure (90), in contrast with ethacrynic acid–treated animals (91). Permanent anoxia preceded by ethacrynic acid injection results in EP values that never reach the values usually obtained with anoxia alone (92). This may be caused by reduced permeability of the cochlear partition to potassium ions (93). CM is reduced after loop diuretics, especially ethacrynic acid, which has a greater effect on the outer hair cells (81). The reduction of the EP by loop diuretics appears to cause a reduction in the spontaneous firing rate of the eighth nerve, perhaps because of a reduction in the continuous release of neurotransmitter (94). Sound-evoked responses of the cochlea are also reduced, including AP (19, 75), evoked activity of single auditory nerve fibers (94, 95), auditory brain-stem response (96), and behavioral responses to sound (97). Furosemide appears to reduce the frequency selectivity of the cochlea, since significant blunting of the sharply tuned tip segment of the tuning curve can take place (94, 95). Loop diuretics abolish cochlear echoes (98). Impedance changes in the cochlear membranes following ethacrynic acid injection have been demonstrated (99) as well as an elevation of the effective resistance to the cochlear partition after furosemide injection (89). Piretanide may be less ototoxic than bumetanide or furosemide, but there may be species variations (75, 88).

Biochemical Effects

The concentration of potassium in endolymph is significantly reduced by ototoxic doses of loop diuretics (92, 100), with a reduction of chloride and elevation of sodium concentration (101).

Initially it was thought that ethacrynic acid inhibited Na,K-ATPase in the stria vascularis, but subsequent experiments have failed to confirm this (84). Adenylate cyclase is present in high concentrations in the stria vascularis and was thought to be a target for loop diuretics (84), but recently it has been shown that this cochlear enzyme is not altered by these agents (102, 103). Loop diuretics appear to block the potassium chloride cotransport system that moves these ions out of the stria vascularis into the endolymph (82, 104).

There have been extensive studies of ethacrynic acid metabolism in relation to ototoxicity. The drug itself (105) or its cysteine metabolite (106) may be the

ototoxic species. A direct correlation has been found between the rate at which thiol conjugates of ethacrynic acid liberate free ethacrynic acid in vitro and their ototoxic potential in guinea pigs (107). Moreover, the diuretic efficacy of a series of thiol adducts of ethacrynic acid parallels their ototoxic potential (107). The ototoxic effects of furosemide may be mediated by a metabolite in premature infants (108). However, it is unclear whether this metabolite, CSA (2-amino-4-chloro-5-sulfamoyl anthranilic acid) is an artifact of the analytical procedure (109). The glucuronide metabolite has been found in both serum and perilymph of chinchillas receiving ototoxic doses of furosemide (86), but it is not known whether this metabolite is ototoxic. The different time course of appearance and disappearance of furosemide glucuronide in serum and perilymph (86) suggests the possibility that the cochlea is a drug-metabolizing organ.

The transfer of loop diuretics from the blood to the kidney lumen depends primarily on an active organic acid transport system in the proximal tubule (110). Similar anion carriers have been demonstrated in other tissues and a similar transport system may exist in the cochlea (111). Ethacrynic acid alters glutathione metabolism in the kidney, but the other loop diuretics do not (112) and it is not known whether glutathione is present in the inner ear.

Interactions

Various studies have demonstrated ototoxic potentiation between loop diuretics and aminoglycosides (19, 22).

The dose-ototoxic response curves for loop diuretics combined with a single dose of kanamycin were found to be parallel, but the relative ototoxic potential of bumetanide was less (113). Noise exposure has been shown to potentiate the damage to the inner ear caused by the aminoglycoside antibiotics, but not that caused by loop diuretics (114).

NONSTEROIDAL ANTI-INFLAMMATORY AND ANTIMALARIAL DRUGS

A hearing loss of 20–40 dB occurs across the audible frequency range in normal-hearing subjects and is preceded or accompanied by tinnitus with blood levels of salicylate in excess of 200–450 mg/liter (115). Auditory symptoms usually disappear within 24–72 hours after cessation of salicylates. Aspirin ototoxicity has been reported to occur in 11 per 1000 patients (77), but a much higher incidence has been reported after use of long-acting aspirin (116). Aspirin in large doses produces temporary changes in psychophysical measures of auditory function in normal human subjects, producing findings that mimicked those seen in subjects with permanent sensorineural deafness (117). Salicylates reach a maximum value in perilymph of 25–33% of the correspond-

ing blood level about two hours after intraperitoneal injection (118, 119). Tritium-labelled salicylate was detected very quickly in the blood vessels of the stria vascularis and spiral ligament (120). Within an hour, the label was found around the outer hair cells and near the spiral ganglion cells, without accumulation in any specific structures (120). Direct perfusion of sodium salicylate reduces AP amplitude (121). Salicylates may inhibit cochlear transaminase and dehydrogenase systems (119) and/or acetylcholinesterase in efferent endings (120). ATP levels of Reissner's membrane of salicylate-intoxicated animals were significantly reduced (122). The ATP and phosphocreatine content of the cochlear nerve and stria vascularis were increased (122). Since nonsteroidal anti-inflammatory drugs are known to inhibit prostaglandin synthesis, depletion of these fatty acids may cause ototoxicity (19). Aspirin has been found to abolish spontaneous otoacoustic emissions in a reversible manner (123). The thresholds of single auditory nerve fibers were rapidly elevated following injection of large doses of sodium salicylate in cats. Fibers became less sharply tuned and there was an increase in spontaneous rate of neuron firing (124).

Because salicylates selectively reduced the AP in experimental animals (125), ultrastructural studies were carried out. No pathological changes of the auditory nerve were seen (126). Other ultrastructural studies of salicylate-intoxicated animals revealed normal cochlear structures (127). Humans with audiometrically documented salicylate-induced hearing loss were found in temporal bone studies to have no significant cellular alterations except those attributed to the age of the patient (128, 129). Salicylates may have a temporary metabolic effect that alters sensory receptor cells or neurons directly, or indirectly by decreased cochlear blood flow (1). Indomethacin-treated guinea pigs were found to have questionable distension of Reissner's membrane, but no ultrastructural abnormalities were detected (130). The auditory brain-stem response of guinea pigs chronically treated with ibuprofen was reported to be normal (131). Five patients were reported to suffer a hearing loss while receiving naproxen; only two recovered hearing after discontinuing the drug (132).

Abortifacient doses of quinine have resulted in deafness of the mother or of the infant when the pregnancy was not terminated (1). Animals given quinine in chronic doses of 50–100 mg/kg/day showed loss of hearing by behavioral testing (133). Histological study showed advanced degeneration of the cochlea, with the greatest injury in the base. Locally applied quinine resulted in reduced cochlear responses, and the outer hair cells and the stria vascularis were damaged (134). Transplacental ototoxicity resulting in deafness has been described in three children of a mother who had no toxic symptoms herself following chloroquine administration (135). Permanent and progressive ototoxicity in a teenager was reported (136). Ototoxicity may be reversed by cessation of chloroquine and the administration of corticosteroids (137). An

autoradiographic study demonstrated accumulation of labelled chloroquine in melanin-containing tissues of the inner ear that persisted for nearly two weeks after injection; thus ototoxicity of chloroquine may be related to uptake by melanocytes in the stria vascularis (138).

Salicylates were found to exacerbate the temporary hearing loss induced by exposure to intense sound (139), but sulindac or diflunisal did not increase the sound-induced hearing loss in human subjects (140). Previous animal studies on the possible interactions of noise exposure and salicylates have produced conflicting results (114).

ANTINEOPLASTIC DRUGS

Cisplatinum is an inorganic platinum coordination complex with marked antineoplastic activity against solid tumors. The major organs affected by toxicity include kidney, bone marrow, gastrointestinal tract, and inner ear. The exact mechanism of cisplatinum-induced ototoxicity has not been defined, but it has been demonstrated that cisplatinum inhibits the activity of adenylate cyclase in cochlear tissues (141). There are morphologic similarities in the pattern of cochlear damage resulting from cisplatinum ototoxicity and due to aminoglycosides. Animal studies have shown that the outer hair cells of the basal turn of the cochlea are damaged first, with eventual damage to more apical cells (142, 143). The first row of outer hair cells appears to suffer the greatest initial damage. Ultrastructural studies showed supporting cell damage, and irregular stereocilia of both inner and outer hair cells were observed (144). Marked degeneration of the stria vascularis has also been observed following cisplatinum injection (145). Recent studies of temporal bones from patients with cisplatinum-induced hearing loss have demonstrated large, fused stereocilia and damaged cuticular plate of the basal outer hair cells, with degeneration of spiral ganglion cells and cochlear neurons (146, 147).

It is difficult to define the exact incidence and severity of cisplatinum-induced auditory defects because of inconsistencies in previous studies and incomplete data from patients too ill to cooperate for hearing tests (148). The incidence of hearing loss following cisplatinum therapy has ranged from 9 to 91% (148). Symptoms that strongly suggest ototoxicity include otalgia, tinnitus, and subjective deafness (149). Hearing loss is usually bilateral, but may be asymmetrical (150), and begins in the higher frequencies (6000 to 8000 Hz). Progression to lower frequencies (2000 and 4000 Hz) may occur with continued therapy (148). Some reversibility may be experienced but when the hearing loss is profound, it appears to be permanent. Higher frequency hearing loss may not be detected without audiometry. Speech understanding may be markedly reduced (151). The critical cumulative ototoxic dose may be 3–4 mg/kg or 100 mg/m^2 (148). Ototoxicity can be more pronounced after bolus injection and

may be minimized by using slow infusion and dividing the doses (152). Hearing loss prior to initiation of cisplatinum therapy may predispose to drug-induced hearing loss (148). Cochlear toxicity may be detected earlier with high-frequency audiometry than with conventional auditory testing (153). Children receiving high doses of cisplatinum (above 540 mg/m^2) have a high incidence of hearing loss (154) that appears to be accentuated by cranial irradiation (155). Animal studies have shown potentiation of cisplatinum-related loss of auditory function and damage to inner and outer hair cells by ethacrynic acid (156) or kanamycin (157).

Other antineoplastic agents have been reported to be ototoxic. Vinblastine destroys hair cells in the organ of Corti, without changing the cells or fibers of the spiral ganglion (158). Vincristine, on the other hand, was found to destroy not only the sensory cells but also the spiral ganglion cells and fibers (159).

Nitrogen mustard has also been reported to be ototoxic. Cats were found to have nearly total loss of hair cells and auditory function following injection of nitrogen mustard (160). The EP and CM were found to decrease rapidly after injection of nitrogen mustard, and then to recover gradually. However, a large (−) SP remained (161). The histological changes produced by nitrogen mustard resemble those produced by aminoglycosides.

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