Paparella: Volume II: Otology and Neuro-Otology

Section 3: Diseases of the Ear

Part 4: Inner Ear

Chapter 46: Ototoxicity

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Ototoxicity has long been recognized as an undesirable side effect of medical treatment and, as new, more potent therapeutic agents are developed, the list of ototoxic drugs continues to grow. As early as the nineteenth century, quinine, salicylates, and oil of chenopodium were noted to produce tinnitus, hearing impairment, and vestibular disturbances (Schwabach, 1884; North, 1880). In 1940, Werner reviewed the early literature and described the ototoxic effects of a variety of agents including arsenicals, ethyl and methyl alcohol, nicotine, bacterial toxins, and heavy metal compounds. With the discovery of the antibiotic streptomycin, the first effective chemotherapeutic agent for tuberculosis, came the realization that it also caused hearing impairment and vestibular disturbances (Hinshaw and Feldman, 1945). Other aminoglycoside antibiotics that subsequently came into clinical use were found to share streptomycin's potential for producing ototoxic side effects (Lerner et al, 1981). The peculiar susceptibility of the inner ear to injury by certain classes of drugs was further demonstrated following introduction of the loop diuretics, which apparently exert their ototoxic influence by a different mechanism of action than the aminoglycoside antibiotics (Thalmann et al, 1982).

Tinnitus, hearing loss, and vertigo are the cardinal symptoms of ototoxicity. Tinnitus usually accompanies acquired sensorineural hearing loss of any cause and frequently precedes and supersedes the hearing loss itself. The tinnitus associated with ototoxicity is typically intense and high-pitched, ranging from 4 kHz to 6 kHz. In the presence of irreversible damage, the tinnitus may, with time, become less severe but typically never disappears. Loop diuretics may provoke intense tinnitus within minutes of intravenous injection. In less severe cases, however, they may produce an insidious, progressive sensorineural hearing loss with only mild tinnitus.

Reversible tinnitus and hearing loss may occur with salicylates and quinine, and the acute hearing loss caused by loop diuretics may recover with prompt cessation of therapy. Transient hearing loss also has been reported with aminoglycoside antibiotics but that loss is more commonly permanent (or only partially recoverable). Hearing impairment due to antibiotic administration usually occurs after 3 to 4 days but may become apparent after the first dose. Permanent ototoxic hearing loss may even be delayed days, weeks, or months after completion of therapy. Bilateral hearing loss predominates, but unilateral loss is not rare.

Ototoxic hearing impairment is exclusively sensorineural. Ototoxic antibiotics typically produce audiometric evidence of a steeply sloping loss in the high frequencies, whereas diuretic-induced ototoxicity usually results in a flat or slightly sloping audiometric pattern.

Disequilibrium of ototoxic origin is most often associated with the administration of gentamicin and streptomycin. Its onset is insidious, with the severity being directly proportional to the duration and quantity of the drug given and to the status of renal function. Disorders of gait and posture predominate, and patients often complain of an inability to stabilize ocular images (oscillopsia), particularly after positional changes. Rotary dizziness is rarely described and does not occur at rest. As patients become increasingly reliant on proprioception and visual input, there is usually gradual accommodation to the vestibular disturbance.

The list of substances suspected of being ototoxic is prodigious. Aminoglycoside antibiotics and loop diuretics are two of the most commonly encountered and potentially dangerous classes of ototoxic drugs. In this chapter, they are therefore discussed in depth, followed by other, less commonly encountered ototoxic agents.

Antibiotics

Aminoglycosides

The association between aminoglycoside therapy and inner ear dysfunction became apparent during the earliest clinical trials, and this association has held true for every aminoglycoside antibiotic introduced. Streptomycin came into clinical use in 1944, followed by neomycin in 1949, paramycin in 1956, kanamycin in 1957, gentamicin in 1963, tobramycin in 1967, and amikacin in 1972. Sisomicin and netilmicin are among the latest aminoglycoside antibiotics to be introduced. Most prospective studies cite a 10 per cent incidence of ototoxicity with aminoglycoside use. The usual hearing loss is bilateral and high-frequency, corresponding to hair-cell loss in the basal turn of the cochlea; however, either unilateral cochlear or vestibular disturbance is possible. The rapidity of onset and degree of hearing loss is usually dose-related and dependent on renal function. The onset of hearing impairment may be detected with high-frequency audiometry within 1 to 2 days of the initial dose. The loss is typically permanent; however, reversal of aminoglycoside-induced changes has been reported in a few cases.

Although the various aminoglycoside antimicrobials are similar in many respects, each is distinct in its spectrum of antibiotic activity and in its ototoxic effect. *Streptomycin* was the first of the aminoglycosides to be clinically employed, especially in the treatment of tuberculosis. It is primarily vestibulotoxic, and so much so that its use is extremely limited at present. Streptomycin has been applied for treatment of intractable Ménière's disease in an effort to destroy the vestibular apparatus while preserving the cochlea (Schuknecht, 1950). Although streptomycin is predominantly vestibulotoxic its reduction product dihydrostreptomycin causes severe cochlear damage and is no longer in clinical use. *Neomycin* produces a high incidence of hearing loss with poor speech discrimination when administered parenterally and is therefore no longer recommended by that route. Neomycin should only be administered orally for bowel sterilization or topically for wound care.

Kanamycin, like neomycin, has its primary effect on the cochlea, producing a characteristic sloping sensorineural hearing loss with rare vestibular injury. High serum

concentration of kanamycin due to large dosage or to renal impairment is an important factor in the development of cochlear damage. Additional factors include any other coexistent form of deafness, acoustic trauma, and the simultaneous use of other ototoxic agents. As with all aminoglycoside antibiotics, hearing loss may occur early in therapy or have its onset several months after completion of drug treatment. Kanamycin may be more likely to cause unilateral hearing loss than other aminoglycoside antibiotics.

Gentamicin has the potential to affect vestibular and cochlear sensory cells in a manner similar to streptomycin. The vestibular disturbances occurs first and are more common clinically. Gentamicin is used widely as a potent antimicrobial against gram-negative bacterial infections. Its ototoxicity was anticipated prior to clinical investigation and confirmed soon thereafter (Jackson and Arcieri, 1971). The incidence of ototoxicity is estimated to be 2 per cent. *Tobramycin* also may cause vestibular and cochlear injury. Vestibular symptoms are less common, and high-frequency, steeply sloping hearing loss is more common than with gentamicin. Although its antimicrobial spectrum is similar to that of gentamicin, its ototoxicity parallels that of kanamycin.

Amikacin is a semisynthetic derivative of kanamycin that may cause hearing loss but is reported to produce a lower incidence of ototoxicity than gentamicin (Lerner et al, 1977). Its antimicrobial activity is similar to that of gentamicin, and it displays a resistance to enzymes that degrade gentamicin and tobramycin. In clinical trials, amikacin has displayed very little vestibular toxicity but has demonstrated a potential for causing unilateral hearing loss similar to that seen with kanamycin.

Netilmicin and *sisomicin* are more recently introduced aminoglycoside antibiotics. While netilmicin displays antimicrobial activity similar to that of gentamicin, its ototoxicity appears to be much less. Initial reports also suggest that sisomicin is much less ototoxic than other aminoglycosides.

Clinical Studies

Hinshaw and Feldman reported deafness associated with streptomycin administration in 1945. The term ototoxicity was first applied (in the adjectival form) to aminoglycosides in a report of a neomycin trial by Waisbren and Spink in 1950 and was subsequently used by Hawkins in 1951 in the title of a paper on hydroxystreptomycin. Vestibular disturbances in tuberculous patients treated with streptomycin were commonplace by 1948, and thorough clinical descriptions of the symptoms were published (Fowler and Seligman, 1947; Jongkees and Hulk, 1950; Northington, 1950). The first complaints by patients were usually blurred vision and motion-induced vertigo, with a sense of continued turning after the motion was terminated. Patients were noted to have a wide-based gait and to display difficulty walking on uneven surfaces or in the dark. Spontaneous and positional nystagmus were absent, and optokinetic nystagmus was normal. A fine nystagmus was commonly elicited on lateral gaze, however. Caloric and rotational responses were noted to be reduced in duration and rate or even absent, but the galvanic response remained, suggesting a peripheral rather than central site of lesion.

Vestibular disturbance typically began after 3 to 4 weeks of intramuscular administration. The vestibular effects were also noted to begin earlier if the streptomycin was given intrathecally or in the presence of renal compromise. As compensation for vestibular loss occurred, particularly in young patients, symptoms were noted to slowly subside even with ongoing drug therapy.

Subsequently, it was noted that the first signs of streptomycin ototoxicity may occur as late as 2 to 6 months after termination of therapy. Documentation of the observation that the vestibular apparatus was usually affected prior to the cochlea was provided by electronystagmographic and audiometric evaluation. Rarely, the cochlear effects may be present prior to, and occasionally at the same time as, the vestibular differences (Serles, 1966). The vestibular and cochlear losses are typically permanent although some hearing may be preserved if ototoxicity is detected early.

Hearing loss has been reported after topical use of neomycin for burns and oral administration for bowel sterilization (Gibson, 1967). Ototoxic serum levels of neomycin have been demonstrated after peritoneal irrigation and topical irrigation of burn wounds and decubitus ulcers with 0.25 per cent neomycin solutions (Myerson et al, 1970; Masur et al, 1976).

In clinical practice, gentamicin and tobramycin cause less inner ear damage than in animal experiments, because of their greater antimicrobial activity, which allows smaller doses and shorter courses of therapy. Tobramycin has been claimed to be less ototoxic than gentamicin in experimental animals, but there is not sufficient evidence to substantiate this claim in humans. Prospective studies of aminoglycoside toxicity by Fee (1980) and Smith and colleagues (1980) revealed similar rates of cochlear injury (10-16 per cent) for tobramycin and gentamicin, whereas the incidence of vestibular injury was found to be 5 per cent for tobramycin and 15 per cent for gentamicin. Lerner and associates (1984) described similar findings in a randomized, blind assessment of gentamicin, netilmicin, and tobramycin, with monitoring of serum levels and renal function. Additionally, a similar therapeutic test of tobramycin and netilmicin demonstrated ototoxic effects in 12 per cent of tobramycin-treated patients, compared with 3 per cent with netilmicin (Lerner et al, 1983). Matz (1986) also found netilmicin to have a relatively low incidence of ototoxicity (at 2 per cent), whereas tobramycin, amikacin, and gentamicin all had an incidence in the range of 13 per cent. Additional human studies have confirmed that netilmicin appears to cause less ototoxicity than other aminoglycosides (Tjernstrom et al, 1982).

The risk of ototoxicity in newborns of mothers treated with aminoglycosides during pregnancy is uncertain. Streptomycin has been shown to cross the placental barrier and appear in fetal blood, although at a lower concentration than in maternal blood (Conway and Birt, 1965). Ototoxic deafness acquired in utero by children whose mothers have been treated with streptomycin and dihydrostreptomycin is said to be uncommon. However, case reports of congenital deafness associated with ototoxic drug administration during pregnancy do exist (Jones, 1973). Aminoglycosides should therefore be used with extreme caution in pregnant patients.

Pharmacology and Pharmacodynamics

All aminoglycosides consist of an amino sugar linked to another moiety via a glycoside bond. Neomycin, kanamycin, gentamicin, and tobramycin are distinct from the streptomycins in that the former contain the base deoxystreptamine, whereas streptomycin and dihydrostreptomycin contain streptidine. Neomycin is different from the remainder of the group in that it has three sugar rings rather than two. Variations in the chemical configuration (ie, the number and placement of basic groups on the various sugars) affect the toxicity as well as the activity of these antibiotics (Yung, 1987).

Aminoglycosides are usually applied topically or administered parenterally, because only 3 per cent of an oral dose is absorbed. Serum levels have been demonstrated to vary widely even among normal volunteers (Kaye et al, 1974). Tissue concentrations are typically one-third that of serum and are affected by many factors, including temperature, pH, electrolyte concentration, oxygen tension, and hematocrit. Penetration of the blood-brain barrier is negligible, except perhaps in neonates; therefore, intrathecal administration is necessary to obtain sufficient cerebrospinal fluid levels. Aminoglycoside antibiotics are not metabolized but rather are excreted almost completely by glomerular filtration, and urine concentrations may rise to 10 times that of the serum. Impaired renal function decreases the excretion of aminoglycosides, thereby increasing the level in the serum and perilymph as well as the risk of ototoxicity and nephrotoxicity (Naunton and Ward, 1959). Furthermore, in the setting of decreased renal clearance, aminoglycosides are cleared more slowly from the perilymph than from the serum, resulting in a prolonged perilymph half-life.

The pharmacodynamics of aminoglycoside antibiotics vary somewhat among species, but the pattern is similar in animals and humans (Federspil et al, 1976). A single aminoglycoside injection results in a serum peak at 1 hour, which falls to negligible amounts at 6 hours. The perilymph level peak is reached slowly over 3 to 6 hours, and the aminoglycoside remains in the perilymph for a considerably longer period, reaching minimal levels in 24 to 36 hours. Half-life values for gentamicin, tobramycin, and amikacin in guinea pig perilymph are 12, 10, and 10 hours, respectively. The half-life of kanamycin in the perilymph is 15 hours, which is 10 times its half-life in the blood. There is a definite correlation between the perilymph aminoglycoside level and the resultant ototoxic damage. The quantity of aminoglycoside in the perilymph is directly proportional to the serum level, allowing for a direct correlation of the extent of ototoxicity with dose administered (assuming normal renal function). If the dosing interval does not allow for adequate renal excretion, then serum and perilymph levels continue to rise. Increases in kanamycin concentration in the perilymph have been demonstrated with repeated daily doses; however, this has not been found to occur with gentamicin or tobramycin. Such accumulation and retention is not found in cerebrospinal fluid or aqueous humor.

Aminoglycoside antimicrobials must reach the inner ear through capillary beds rather than via the cerebrospinal fluid, because cerebrospinal fluid levels are low even with high serum levels (Hawkins et al, 1950). Tritium-labeled dihydrostreptomycin injected intraperitoneally in guinea pigs is present in the vessels of the spiral ligament and the stria vascularis within 15 to 30

minutes. It enters the perilymph from the spiral ligament and subsequently enters the endolymph and organ of Corti (Balogh et al, 1970). Portmann and colleagues (1974) demonstrated tracer in Deiters' cells in 1 hour and in outer hair-cells after 4 hours following carotid injection. Labeled dihydrostreptomycin has been observed to accumulate in inner and outer hair-cells following direct cochlear perfusion (Von Ilberg et al, 1971). More recently, Veldman and coworkers (1987) utilized an immunocytochemical technique to localize gentamicin in guinea pig outer hair-cells following intraperitoneal injection of the drug.

Mechanism of Action

There have been several proposals regarding the mechanism of aminoglycoside ototoxicity. After streptomycin treatment, damage has been observed in the stria vascularis as well as in the neuroepithelia of the cochlea and vestibular apparatus. Hawkins (1973) proposed that aminoglycoside exposure results in injury to the secretory and reabsorptive tissues of the labyrinth, thereby disturbing microhomeostasis, with subsequent injury to the sensory cells. Depletion of succinic acid dehydrogenase has been observed in the stria vascularis during dihydrostreptomycin treatment, before any change occurs in the organ of Corti, prompting the suggestion that hair-cell loss occurs as a result of impaired respiratory metabolism in the stria (Musebeck and Schatzle, 1962). There is also some anatomic evidence that degeneration in the lateral wall tissues may precede cochlear hair-cell loss. In addition, the two-phase reduction in the human electrocochlear response following administration of tobramycin supports the hypothesis of an early strial effect (Wilson and Ramsden, 1977).

However, much of the available evidence now points toward a direct influence of aminoglycosides on the hair-cells of the cochlea and vestibular apparatus. These antibiotics apparently exert an immediate physiologic effect on the transduction of sensory input by reversibly blocking calcium-sensitive potassium channels on the apical aspect of the receptor cell (Lim, 1986). This short-term effect may explain the reversible suppression of cochlear microphonics produced by application of aminoglycosides. Eventual degeneration of the sensory cells is believed to be due to inhibition of the synthesis of structural proteins and/or interference with cell membrane lipid metabolism.

The antimicrobial effect of aminoglycoside antibiotics depends on their ability to inhibit protein synthesis via interaction with the 30S ribosomal subunit (Benveniste and Davies, 1973). Some evidence for an influence on protein synthesis in mammalian hair-cells also exists, based on the ultrastructural findings indicating that ribosomal synthesis is disturbed by aminoglycosides (Lim, 1986).

In addition, Schacht and colleagues have proposed interference with cell membrane lipids as a major factor underlying aminoglycoside injury of the inner ear. Specifically, these antibiotics have been shown to inhibit polyphosphoinositide metabolism, which is essential for control of cell membrane permeability and maintenance of membrane structures (Schacht, 1976; Stockhorst and Schacht, 1977; Schacht, 1985).

Thus, as Lim (1986) pointed out in a review on ototoxicity, it seems likely that aminoglycosides produce their effects on inner ear sensory cells by at least two different mechanisms. The first of these is reversible blockage of transduction channels on the apical portion of the hair cell; the second mechanism involves irreversible damage of the biochemical machinery necessary for cell maintenance and survival.

Histopathology

The histopathology of aminoglycoside ototoxicity has been well described and was investigated shortly after the clinical introduction of streptomycin. Initial studies of streptomycin-treated patients and animal experiments suggested various brain stem or cerebellar sites as the ototoxic target areas (Molitor et al, 1946; Stevenson et al, 1947; Winston et al, 1948). Subsequent experimental animal and human temporal bone studies revealed unmistakable destruction of the cochlear and vestibular neuroepithelia, clearly establishing the peripheral site of injury as opposed to the central nervous system (Hawkins and Lurie, 1952; McGee and Olszewski, 1962; Wersall, 1981). The same peripheral toxicity has been identified for all of the aminoglycoside antibiotics.

Structural alterations of the vestibular apparatus associated with aminoglycoside ototoxicity are primarily localized to the hair-cells of the crista ampullaris and the maculae of the saccule and utricle (Wersall and Hawkins, 1962; Koegel, 1985). Although type I hair-cells show greater sensitivity to damage, both type I and type II sensory cells are affected. Ultrastructural changes seen early in the process of hair-cell degeneration include mitochondrial swelling and formation of osmiophilic dense bodies termed "myelin figures" (so-named because of their electron microscopic resemblance to myelin lamellae). Decreased numbers of ribosomes, vacuolated cytoplasm, and nuclear distortion are also observed in damaged hair-cells. Changes seen in severely affected sensory cells include nuclear pyknosis, aberrations of stereocilia, and extrusion of cytoplasm with subsequent cell death (Wersall and Hawkins, 1962; Duvall and Wersall, 1964).

In the cochlea, the ototoxic effects of aminoglycosides are usually first seen in the outer hair-cells of the basal turn (Duvall and Quick, 1969; Darrouzet and Guilhaume, 1974). With increasing severity of damage, degenerative changes extend to include the upper cochlear turns, and inner hair-cells may also be affected. In addition, varying degrees of atrophy of the stria vascularis may be observed in conjunction with alterations of the hair-cells.

Early changes in the sensory cells include the appearance of multivesicular bodies, lysosomes, and myelin figures in the supranuclear portion of the cytoplasm. As degeneration advances, there is clumping of nuclear chromatin, formation of giant, fused stereocilia, and, finally, extrusion of the cell contents. These alterations may eventually lead to destruction of all outer hair-cells throughout the organ of Corti. In cases of relatively mild injury, the inner hair-cells may remain normal or show only minor cytoplasmic alterations. When toxicity is severe, however, the inner hair-cells and supporting structures are also destroyed, resulting in collapse and disappearance of the organ of Corti. Destruction of the neuroepithelium is followed by degeneration of nerve fibers in the osseous spiral lamina and atrophy of the spiral ganglion.

In cases in which the cochlear damage is somewhat less severe, there may be loss of varying numbers of hair-cells with survival of the supporting cells of the organ of Corti. In such instances, defects of the reticular lamina, which occur as a result of sensory cell degeneration, are repaired by expansion of the phalangeal plates of Deiters' cells. This process results in the pattern of so-called "phalangeal scars" seen in wholemount or "surface" preparations of the organ of Corti (Hawkins and Johnsson, 1976).

The use of surface preparations in combination with light microscopy makes it possible to obtain quantitative estimates of cochlear injury by counting missing hair-cells and constructing graphic plots, called cytocohleograms, that show the numbers and locations of missing hair-cells along the length of the basilar membrane from base to apex of the cochlea. Beginning with Engstrom and coworkers in 1964, cytocochleograms have been used by many investigators to document hair-cell loss following the administration of aminoglycoside antibiotics. In most such studies, the general sequence of alterations outlined above (beginning with degeneration of outer hair-cells in the basal cochlear turn) has been confirmed after aminoglycoside administration in experimental animals.

According to some investigators, there is generally little damage to the spiral ligament, the stria vascularis, and the pericapillary tissues of the spiral prominence following experimental administration of aminoglycosides. However, there are several reports of injuries to all of these structures with kanamycin as well as with other aminoglycoside antibiotics (Hawkins, 1976; Johnsson and Hawkins, 1972). Specifically, atrophic changes in the stria with reduction to half its normal size have been described, especially with aminoglycosides possessing strong nephrotoxic potential such as gentamicin and neomycin. In addition, degenerative changes have been reported in the dark cells of the crista ampullaris in experimental animals after treatment with streptomycin or gentamicin (Hawkins and Preston, 1975). These cells are found on the slopes of the cristae and the wall of the utricle and are believed to be responsible for regulation of the composition of vestibular endolymph.

Delayed damage to the organ of Corti after termination of treatment has been documented for dihydrostreptomycin, gentamicin, and tobramycin (Theopold, 1977). Degeneration of neurons has been demonstrated several years after inner and outer hair-cell loss induced by kanamycin (Kiang et al, 1976). However, at the initial time of injury the nerve fibers in the osseous spiral lamina remain intact even with severe hair-cell injury (Johnsson et al, 1981).

Prevention

Aminoglycoside ototoxicity is potentiated by many factors, including renal impairment, prior noise exposure, advanced age, previous aminoglycoside therapy, fever, any prior hearing loss, and the simultaneous use of other ototoxic agents. Specifically, the concomitant use of furosemide, ethacrynic acid, mannitol, and mercurials has been shown to cause potentiation (Brummett et al, 1975; Thomsen, 1976).

Early ototoxicity may be detected by daily audiometry and electronystagmography (ENG). Although bedside audiometry is possible, it is not always practical. Furthermore, with conventional pure-tone audiometry, the loss may be detected only after it is too late to be reversed. Since the initial ototoxic effect is usually in the basal turn (and the corresponding high frequencies), ultra-high-frequency audiometry has been touted as a method to uncover hearing loss while it is still reversible. In clinical experiments, early high-frequency hearing loss has been detected by electrocochleography with mild subclinical changes occurring from 2 minutes to 1 hour after drug administration. These changes, which are potentially reversible, occur even with safe therapeutic levels (Wilson and Ramsden, 1977). Fausti and colleagues (1984) also demonstrated early changes in high-frequency audition before changes in conventional audiometry could be demonstrated, providing earlier detection to allow termination of therapy. The fact remains that, even with early detection, aminoglycoside ototoxicity may occur and even progress after termination of therapy. Monitoring of streptomycin and gentamicin ototoxicity with ENG has been advocated as a method to detect early changes in function prior to the onset of cochlear injury (Serles, 1966). However, ENG monitoring of the patient population at risk - typically, seriously ill patients with chronic renal failure - is very difficult. Positional nystagmus was found to be, and still is, a sensitive early sign of vestibular injury. However, this may be obscured by the effect of pain medications and sedatives.

Attempts to find an agent to antagonize or prevent aminoglycoside-induced injury have been disappointing to date. Use of the pantothenate (rather than the sulfate) forms of streptomycin and dihydrostreptomycin in cats was not effective in reducing ototoxicity (Hawkins et al, 1957). This was confirmed in tuberculosis patients treated with the pantothenate and sulfate forms of dihydrostreptomycin (Glorig, 1958). In addition, the streptomycin-calcium chloride complex was found to be no less vestibulotoxic than the hydrochloride and sulfate forms. Vitamins A and B, mercaptoethylamine, and dimercaptopropanol were also unsuccessful in reducing ototoxicity (Hawkins et al, 1957). Subsequent investigations have demonstrated that vitamin B complex, amino acids, and dexamethasone are ineffective in protecting guinea pigs from kanamycin-induced inner ear injury (Darrouzet, 1967). Various polyanions have been reported to reduce ototoxicity by keeping perilymph antibiotic levels low, but these generally reduce the antimicrobial activity, thereby requiring larger doses for treatment (Stupp et al, 1973).

The mainstay of aminoglycoside ototoxicity prevention continues to be the monitoring of serum levels. Absence of sufficiently low trough levels for adequate periods daily has been shown to be an important determinant of ototoxicity (Nordstrom et al, 1973; Jackson and Arcieri, 1971). In addition to elevated serum levels, treatment for longer than 10 days has been established as another risk factor (Koegel, 1985). In clinical studies with gentamicin in patients with renal failure, ototoxic effects were minimized with longer dosing intervals. However, the efficacy of antimicrobial therapy may be compromised by this strategy. Prediction of proper dosage of gentamicin on the basis of sex, age, weight, creatinine, BUN, and hematocrit in renal failure has been unsatisfactory (Barza et al, 1975). Despite close monitoring of serum aminoglycoside levels, inner ear injury continues to occur frequently.

Erythromycin

The recent use of erythromycin for treatment of *Legionella pneumophila* has resulted in its increased intravenous use, and subsequently reports of its ototoxicity have increased. Symptoms of erythromycin ototoxicity are subjective hearing loss, blowing tinnitus, and occasionally vertigo.

Threshold ototoxic blood concentrations are unknown, but ototoxic serum levels in one patient were 63 to 78 mg/liter (Taylor et al, 1981) and 100 mg/liter in another (Kroboth et al, 1983). The serum half-life is prolonged in patients with renal failure, and serum levels may be three to five times higher than predicted for patients with normal renal function (Kroboth et al, 1983).

The first clinical case of hearing loss due to erythromycin was reported by Mintz and associates in 1973. Additional cases of partial and reversible hearing loss with rapid intravenous erythromycin infusion were subsequently documented (Eckman, 1975; Karmody and Weinstein, 1977). Between 1973 and 1984, 32 cases of bilateral high-frequency sensorineural hearing loss and tinnitus associated with high-dose intravenous or oral erythromycin were reported (Schweitzer and Olson, 1984). Otoneurologic changes are potentially reversible following cessation of therapy, but it is not known whether permanent damage will ensue if the treatment is continued after the onset of auditory symptoms. The mechanism of erythromycin ototoxicity is unknown.

Conditions predisposing to hearing loss resulting from erythromycin therapy include advanced age, hepatic or renal failure, and Legionnaire's disease, increased risk is also reported with a dose greater than 4 grams per day, and the typical interval to the onset of symptoms is 4 days (Haydon et al, 1984). Guidelines for the prevention of hearing loss include limiting the daily dose to less than 1.5 grams if the serum creatinine concentration is above 180 moles/liter and exercising caution with other ototoxic drugs. Pretreatment and post-treatment audiograms are also recommended, especially in elderly patients or in the setting of hepatic or renal failure (Schweitzer and Olson, 1984).

Other Antibiotics

Vancomycin, a narrow-spectrum antibiotic effective against gram-positive cocci, has been reported sporadically to be ototoxic, but usually in cases complicated by renal failure and usage of other antibiotics (Geraci et al, 1958). There has been little experimental evaluation of vancomycin ototoxicity. Vancomycin probably exerts its antimicrobial action by inhibiting cell wall synthesis, in which case it would not be expected to be toxic to human cells. Therefore, it is assumed to have additional mechanisms of cell injury.

There have been occasional reports of ototoxicity associated with several other antibiotics. *Viomycin* is a non-aminoglycoside antibiotic with antituberculous activity, due to its ability to inhibit protein synthesis. Cochlear and vestibular damage does occur in association with viomycin

administration, especially with excessive dosage, prolonged use, or renal compromise (Quick, 1980). *Capreomycin* is another protein synthesis inhibitor with antituberculous activity that has been reported to cause cochlear and vestibular damage with excessive amounts or extended use, especially in association with renal insufficiency (Quick, 1980).

Minocycline is a semisynthetic derivative of tetracycline, which occasionally causes severe vestibular symptoms; nausea, vomiting, and the inability to walk predominate, with nystagmus being absent. The disturbance is typically reversible (Williams, 1974).

Ampicillin and *chloramphenicol* have been associated with hearing loss when employed to treat *Hemophilus influenzae* meningitis (Svenungsson, 1976). The possibility of a simple post-meningitis hearing loss remains. Numerous other antibiotics, including ristocetin, polymyxin B, pharmacetin, and colistin have been implicated as potential ototoxic agents. Most of these agents are no longer administered systematically because of their toxicity.

Loop Diuretics

Ethacrynic acid, furosemide, and *bumetanide* are potent natriuretic agents that are known as loop diuretics because they inhibit the reabsorption of electrolytes and water in the ascending limb of the loop of Henle. Although these agents have few side effects, they do show considerable ototoxic potential, especially when administered intravenously in patients with renal insufficiency. The hearing impairment produced by ethacrynic acid and furosemide is most often transient, but it is now recognized that both agents may produce permanent hearing loss in exceptional cases (Pillay et al, 1969; Rybak, 1982).

The newer loop diuretic bumetanide has been reported to be less ototoxic than ethacrynic acid and furosemide. In a series of 179 patients treated with bumetanide and 62 patients treated with furosemide, the incidence of hearing loss of 15 dB or more measured pure-tone audiometry was reported as 1.1 per cent with bumetanide and 6.4 per cent with furosemide (Tuzel, 1981).

Pharmacology and Pharmacodynamics

Ethacrynic acid is a phenoxyacetic acid derivative, whereas furosemide is a relative of the sulfonamides. Gastrointestinal uptake of furosemide approaches 65 per cent following oral administration, and it is excreted largely in the urine (Prandota and Pruitt, 1975). The average half-life for renal excretion is about one-half hour, but this may be prolonged in renal failure for up to 10 to 20 hours. Plasma levels greater than 50 mg/mL have been associated with hearing loss (Wigand and Heidland, 1971).

Mechanism of Action

Multiple mechanisms have been proposed to account for loop diuretic ototoxicity. All loop diuretics prevent resorption of sodium and chloride, and hence of water, in the ascending loop of Henle and to a lesser extent in the distal convoluted tubule. Proposed mechanisms for renal

diuretic effects include inhibition of sodium-potassium ATPase, reaction with protein-bound sulfhydryl groups, and a direct effect on energy metabolism in the mitochondria (Suki et al, 1973). Burg and colleagues (1973) suggested a more direct effect on chloride rather than sodium transport. This idea was supported by other workers who found that furosemide inhibits active resorption of chloride in the distal segment of the loop of Henle, thereby preventing resorption of sodium, which passively follows chloride (Benet, 1979).

The biochemical mechanisms involved in diuretic action are presumed to be the same as those involved in producing strial pathology and thereby ototoxicity. Loop diuretic inhibition of cochlear sodium-potassium ATPase has in fact been cited as a cause of ototoxicity (Prazma et al, 1972). This possibility is supported experimentally by the observed increase in sodium concentration in the endolymph following ethacrynic acid administration. Additionally, the possibility that carbonic anhydrase activity is adversely affected has also been proposed (Brown, 1973); however, inhibition of carbonic anhydrase by administration of acetazolamide does not produce ototoxic effects similar to those seen after application of ethacrynic acid (Mendelsohn and Mittelman, 1971). Several investigators have noted that furosemide and ethacrynic acid, at concentrations that inhibit the endocochlear potential, are potent inhibitors of the cochlear enzyme adenylate cyclase (Kerr and Schacht, 1975; Paloheimo and Thalmann, 1977; Kusak-ari et al, 1978). The concentration of ethacrynic acid required to reverse the sign of the endocochlear potential has been observed to be the same as that producing 50 per cent inhibition of adenylate cyclase in mouse brain, whereas a higher concentration is required to inhibit sodium-potassium ATPase (Ahlstrom et al, 1975). Subsequent workers were unable, however, to support a role for alteration of adenylate cyclase metabolism in loop diuretic ototoxicity but reiterated a clear influence on ion pumps in the cochlea as well as the kidney (Marks and Schacht, 1981; Thalmann et al, 1982).

Animal Studies and Histopathology

The loss of the Preyer reflex has been demonstrated within 6 minutes of intravenous injection of high-dose ethacrynic acid in guinea pigs, with hearing loss being dose-dependent (Quick and Duvall, 1970). After one dose of ethacrynic acid, return of hearing starts at 7 hours, and Preyer's reflex has returned completely by 16 hours. Electrophysiologic confirmation of rapid hearing loss following intravenous injection of ethacrynic acid, furosemide, and bumetanide has been provided by many investigators (Brummett et al, 1977; Brown, 1975).

Histopathologic studies reveal injury primarily limited to the stria vascularis, followed by hair-cell changes. The predominance of strial injury correlates with the flat sensorineural hearing loss as predicted by Schuknecht's (1974) hypothesis for strial atrophy. Characteristic strial changes were noted in an experimental animal study by Quick and Duvall (1970), who found accumulation of fluid in the stria vascularis and an overall increase in strial width. The amount of strial distention was found to be proportional to the amount of drug given. Ultimately, total strial degeneration was observed. Ultrastructural hair-cell changes, particularly in the basal turn, were demonstrated, but not as consistently as with aminoglycoside antibiotics. Hair-cell pathology was also noted to be dose-dependent. Similar findings have been produced by furosemide, with

strial effects predominating (Quick and Hoppe, 1975; Brummett et al, 1977). In a 1981 study, Arnold and associates examined the temporal bones of a patient treated with 5000 milligrams of furosemide and 250 milligrams of ethacrynic acid over 5 days prior to death from renal failure and found no changes in the inner and outer hair-cells at either the light or electron microscopic level. The stria vascularis showed marked cystic changes similar to those previously reported in animal studies. The dark cell areas of the vestibular apparatus also exhibited cystic changes, with dilation of intercellular fluid spaces, suggesting an effect on inner ear fluid transport.

Prevention

Most cases of severe loop diuretic ototoxicity occur in the clinical setting of advanced renal failure along with concurrent administration of ototoxic antibiotics. Rapid intravenous infusion of large doses of furosemide is a prime factor underlying permanent hearing loss. Therefore, rapid intravenous push administration of the drug is not recommended. Furthermore, furosemide should be used with extreme caution in the face of increasing azotemia and oliguria.

The concomitant administration of aminoglycoside antibiotics is a major risk factor in loop diuretic-induced ototoxicity, and summation and potentiation of ototoxic effects have been demonstrated in experimental animals and in humans. Synergistic ototoxic effects are well described in the literature (Mathog and Klein, 1969; Meriwether et al, 1971). Strial damage has been shown to increase the entrance of ototoxic antibiotics into cochlear fluids, thereby potentiating their ototoxic effects (Brummett et al, 1975; West et al, 1973). A single dose of kanamycin with intravenous ethacrynic acid has been observed to cause extensive damage to the organ of Corti, whereas neither alone has any permanent effect on cochlear function (West et al, 1973). The effect is seen only when the drugs are administered within an hour of each other. The injuries consist of severe but apparently reversible strial edema, followed at 2 days by destruction of hair-cells. This breakdown of the hemolabyrinthine barrier to kanamycin by ethacrynic acid underscores the need for caution in the concurrent use of diuretics and aminoglycoside antibiotics (Hawkins and Preston, 1975).

Anti-Inflammatory Agents

Salicylates have long been associated with tinnitus and occasionally with sensorineural hearing loss and therefore should be regarded as ototoxic agents. However, salicylates are unique in that their effects are usually reversible and not associated with demonstrable morphologic injury. Aspirin (acetylsalicylic acid) in high doses produces tinnitus and high-frequency sensorineural hearing loss, both of which are reversible with termination of therapy. Tinnitus and deafness usually occur in the setting of salicylism but may occur with therapeutic use in rare cases. Sporadic reports have also appeared in the literature describing the ototoxic effects (primarily reversible tinnitus and hearing loss) of non-steroidal anti-inflammatory agents such as indomethacin, ibuprofen, and piroxicam.

Clinical Studies

The characteristic tinnitus and hearing dysfunction associated with salicylate therapy have been described as appearing early in the treatment of rheumatoid arthritis and disappearing with termination of drug dosage. Audiologic studies have revealed sensorineural hearing loss as great as 30 to 40 dB at all frequencies, with return to normal hearing after withdrawal of salicylates (McCabe and Dey, 1965). Audiometric site of lesion studies on salicylate toxicity point to a cochlear rather than a central effect. Additionally, depression of vestibular response by aspirin has been described (Bernstein and Weiss, 1967). There are also scattered reports of permanent hearing loss (Waltner, 1955; Kapur, 1965). In 1884, Schwabach described a case of permanent hearing loss following a therapeutic salicylate dose and a case of persistent tinnitus caused by quinine but exacerbated by sodium salicylate. Permanent hearing loss has been documented in survivors of salicylate poisoning (Jarvis, 1966). Piroxicam has also been recently reported to be responsible for a case of permanent hearing loss (Vernick and Kelly, 1986).

Experimental Studies

Salicylates are rapidly absorbed following oral ingestion and quickly enter the perilymph after systemic injection. Perilymph concentrations of salicylates may reach levels as high as one-fourth that of the serum level in cats and chinchillas following intraperitoneal injection (Juhn et al, 1985). There is some evidence in rats and guinea pigs of active transport of salicylate into the perilymph rather than a simple filtration of salicylate from the cerebrospinal fluid into the perilymph (Jastreboff et al, 1986). Autoradiographic studies have revealed tritium-labeled salicylate in the blood vessels of the stria vascularis and spiral ligament within minutes after systemic administration. Within 1 hour, it is detectable around the outer hair-cells and also in Rosenthal's canal (Ishii et al, 1967).

Sodium salicylate has been shown to selectively reduce cochlear action potential response in experimental animals (Mitchell et al, 1973). This is an agreement with previous findings of Silverstein and associates (1967) who demonstrated a greater drop in N1 action potential than in the microphonic potential with salicylate toxicity. Koopman and coworkers (1982) found no change in auditory evoked brain stem response in guinea pigs treated daily with doses of ibuprofen comparable to human therapeutic doses. With the possible exception of vasoconstriction of the capillaries of the spiral ligament and stria vascularis (Hawkins, 1973a), no consistent histopathologic changes have been demonstrated in cochlear tissues following administration of salicylates or other nonsteroidal anti-inflammatory agents.

The inability to demonstrate morphologic alterations responsible for the reported hearing loss and tinnitus of nonsteroidal anti-inflammatory agents corroborates the clinical phenomenon of reversibility of hearing loss and suggests that salicylates have some temporary metabolic effect not severe enough to kill sensory or receptor cells. Kirchner (1881) and Blau (1904) proposed vasomotor disturbances and ischemia as the cause of salicylate ototoxicity. More recently, it has been suggested that salicylates may have an indirect influence on cochlear microvasculature by way of their effect on prostaglandin synthesis (Hawkins, 1976).

In biochemical studies on effects of salicylate administration, Silverstein and colleagues (1967) demonstrated decreased malic dehydrogenase activity in the endolymph and the perilymph as well as increase glucose concentrations. No changes were found in sodium, potassium, or total protein content. On this basis, they proposed salicylate inhibition of transaminase and dehydrogenase systems, thereby interfering with the transfer of hydrogen by diphosphopyridine nucleotide.

Antimalarial Agents

Both temporary and permanent sensorineural hearing losses have been reported with the antimalarial drugs quinine and chloroquine. As early as 1696, temporary deafness was recognized as a side effect of the use of cinchona bark (the natural source of quinine) for treatment of fevers. In 1843, Melier noted that deafness due to quinine use disappeared quickly with small to moderate doses but tended to become permanent if large doses of quinine were taken. Tinnitus and hearing loss were well-documented side effects of quinine treatment before the end of the nineteenth century (Schwabach, 1884).

In current clinical practice, hearing loss and tinnitus are most commonly seen in elderly patients using large doses of quinine for leg cramps. Small doses may even cause tinnitus in susceptible patients, but permanent deafness is rare. However, permanent deafness has been reported with the use of chloroquine (Toone et al, 1965). Quinine and chloroquine both cross the placenta and there are case reports of congenital hearing loss and cochlear hypoplasia associated with their use in pregnancy (Hart and Naunton, 1964).

Experimental Studies

In 1875, Roosa and John observed vascular congestion in the tympanic membrane vessels with quinine therapy and attributed the tinnitus and deafness to a similar "congestion of the terminal fibers of the auditory nerve in the cochlea". Other early investigators postulated that the quinine effect on the inner ear was caused by vasoconstriction comparable to the retinal ischemia seen in quinine-treated animals (Wittmaack, 1903).

Early histopathologic studies revealed changes in the mitochondria of cochlear hair-cells, along with vascular stasis and distention of the stria vascularis (Covell, 1938). Ruedi and associates (1952) noted cystic degeneration of the stria vascularis, hair-cell loss, and degeneration of cochlear neurons following long-term administration of quinine. Such changes have been confirmed in more recent studies, which have shown that the degenerative effects are most severe in the basal cochlear turn (Koegel, 1985). Guinea pigs acutely intoxicated with quinine, quinidine, or sodium salicylate have shown vasoconstriction in the capillaries of the suprastrial spiral ligament, stria vascularis, and basilar basement membrane. Local narrowing of the capillary lumen by endothelial cell swelling similar to that seen in noise exposure has been noted (Hawkins, 1973). Lawrence (1970) also demonstrated vasoconstriction after quinine injection during in vivo microcirculatory studies of the guinea pig cochlea, supporting previous inferences concerning the role of ischemia in quinine ototoxicity.

Antineoplastic Agents

Several antineoplastic drugs have been associated with hearing loss. Cis-platinum, a cytoreductive agent employed in the treatment of a variety of neoplasms, is the most thoroughly investigated of the group. The potential usefulness of this agent is limited by ototoxicity and nephrotoxicity. Various other antineoplastic agents, including bleomycin, 5-fluorouracil, and nitrogen mustard, have been implicated in ototoxicity as well. The definition of incidence and severity of ototoxicity is difficult because of inconsistent studies and lack of complete audiometric documentation in a debilitated population.

Cis-Platinum

Clinical Studies

The symptoms most commonly associated with cis-platinum ototoxicity are subjective hearing loss, tinnitus, and otalgia (Reddel et al, 1982) but may also include vestibular disturbances in rare cases (Schaefer et al, 1981; Black et al, 1982). The hearing loss is typically bilateral, first at frequencies of 6 and 8 kHz, and then progressing to involve lower frequencies (Helson et al, 1978). Tange and colleagues (1985) reported a series of 23 patients treated with cis-platinum in which eight patients developed significant auditory changes above 8 kHz. This high-frequency hearing loss may result in markedly reduced speech discrimination scores by the time the ototoxicity is detected (Rybak, 1981). Occasionally, an asymmetric hearing loss may occur. In addition, the hearing loss may only appear several days after discontinuation of treatment. There may be some degree of reversibility of mild hearing loss, but when profound hearing loss occurs, it is usually permanent. Tinnitus is often transient, lasting a few hours to a few weeks after termination of therapy. Pretreatment and post-treatment objective vestibular studies have confirmed the occurrence of vestibular toxicity (Komune et al, 1981). The incidence of cis-platinum-induced hearing has been reported to be as high as 91 per cent (Helson et al, 1978) and as low as 9 per cent (Higby et al, 1974).

The critical cumulative dose for cis-platinum ototoxicity has been reported as 3 to 4 mg/kg of body weight (Hayes et al, 1977). However, the critical cumulative dose is difficult to ascertain, owing to the inclusion of heterogeneous tumor populations, application of multiple-agent therapy, use of different methods of drug administration, and inclusion of patients with histories of other ototoxic drug exposure. A prospective study (Schaefer et al, 1985) of 24 patients with head and neck tumors, selected for uniformity of chemotherapy regimen, renal status, and lack of prior or concurrent exposure to ototoxic drugs, suggested an increased risk of ototoxicity with a cumulative cis-platinum dose of more than 400 mg. In addition, hearing loss was found to be primarily high-frequency, dose-related, and irreversible. Vestibular toxicity was documented in only one patient. More severe hearing loss has been reported in patients receiving cranial radiation prior to cis-platinum therapy, suggesting a synergistic ototoxic effect (Granowetter et al, 1983).

Strauss and colleagues (1983) compared clinical findings with temporal bone histopathology in a group of patients who received cis-platinum chemotherapy. They reported hearing loss in 25 per cent of patients at 4 kHz and 8 kHz; the loss, however, did not exceed 25 dB at any frequency. Examination of temporal bones from a 9-year-old patient revealed marked loss of outer hair-cells affecting all three rows in the basal cochlear turn, with some degeneration of inner hair-cells in the basal and middle turns. In addition, extensive wallerian degeneration of the cochlear nerve was observed, whereas vestibular neurons were found to be normal. A scanning electron microscopic study of temporal bone material by Wright and Schaefer (1982) showed giant, fused stereocilia and damage to outer and inner hair-cell cuticular plates, following cis-platinum administration.

Experimental Studies

A pattern of morphologic damage rather similar to that seen in aminoglycoside antibiotic-induced injury has been reported in a number of experimental studies on cis-platinum ototoxicity. Histopathologic studies utilizing rodents and primates have demonstrated loss of hair-cells that is most severe in the basal turn of the cochlea (Fleischman et al, 1975; Stadnicki et al, 1975). The first row of outer hair-cells is typically found to be the most damaged (Schweitzer et al, 1984). Ultrastructural changes found in guinea pig outer hair-cells after cis-platinum administration have included dilatation of subsurface cisternae, softening of cuticular plates, vacuole formation, and increased numbers of lysosome-like bodies (Estrem et al, 1981).

Schweitzer and associates (1984) demonstrated potentiation of the ototoxic and nephrotoxic effects of cis-platinum by concomitant administration of low doses of kanamycin in guinea pigs. Their study provided evidence that combined therapy with cis-platinum and aminoglycosides in cancer patients may significantly increase the risk of renal damage and sensorineural hearing loss.

Prevention

High-frequency audiometry may detect cochlear injury from cis-platinum earlier than conventional audiometry and may be helpful as a monitor of ototoxicity. The potential for ototoxicity with cis-platinum is increased with renal impairment, rapid dosing, volume depletion, and the use of other ototoxic agents. Cis-platinum ototoxicity may be more pronounced with bolus administration, and may be reduced by slow infusion divided over several months (Higby et al, 1974). Thiosulfate has been observed to be protective against the toxic effects of cis-platinum in guinea pigs (Otto et al, 1987).

Topical Ototoxic Agents

In recent years there has been growing concerns regarding the use of antiseptic agents, chemical solvents, and antimicrobials that may be ototoxic if applied to the middle ear cavity. Topical otic preparations now employed in the management of ear disease typically contain one or more ototoxic antibiotics in combination with anti-inflammatory agents and various solvents.

The use of such preparations in patients who have tympanostomy tubes or tympanic membrane perforations has been questioned, since there is evidence that these agents can enter the middle ear cavity and eventually damage the membranous labyrinth. Antiseptics such as chlorhexidine and povidone-iodine, used in preoperative skin preparation, have also been implicated in hearing loss (Bicknell, 1971; Morizono and Sikora, 1983), as has ethyl alcohol, which is widely used as a disinfectant, either alone or in combination with other antiseptics (Morizono and Sikora, 1981). There has also been some suggestion that degeneration of Gelfoam may produce formaldehyde, the ototoxic effects of which may adversely affect the inner ear (Quick, 1980).

It is generally believed that toxic materials in the middle ear cavity gain access to the inner ear by diffusion and pinocytosis across the round window membrane, which has been shown to be permeable to a wide range of substances of varying molecular weight and size (Goycoolea et al, 1980; Tanaka and Motomura, 1981). Several investigators have demonstrated that antibiotics such as neomycin, gentamicin, and kanamycin do reach the perilymph if they come into contact with the round window membrane in experimental animals (Stupp et al, 1973; Smith and Myers, 1979; Harada et al, 1986). In one of the more recent of these studies, Harada and colleagues (1986) found high concentrations of neomycin in cochlear perilymph within 30 minutes of its application to the lateral side of the guinea pig round window membrane, and structural damage of the organ of Corti was apparent within 4 hours.

The ototoxic properties of the aminoglycosides are, of course, well established. However, some antimicrobials, such as chloramphenicol and polymyxin B, which are not consistently ototoxic when administered systemically, have been found to produce severe inner ear damage when placed in the middle ear cavity (Stupp et al, 1973; Parker and James, 1978).

In some experimental studies of topical antibiotics and antiseptics, relatively high concentrations of the test substances have been applied to the middle ear cavity, so that the resulting toxic effect hardly seems surprising. However, many agents have proved to be deleterious to the inner ear when applied to the tympanic cavity in experimental animals at concentrations comparable to those used in clinical practice.

Such toxic effects may be considerably increased if several ototoxic agents are combined in a single preparation, as is done in the formulation of various otic drops designed to be effective against a broad spectrum of microorganisms. Although most of these preparations are designed for treatment of otitis externa, they have frequently been used in patients who have perforated tympanic membranes. In such cases, the drops may enter the middle ear cavity and contact the round window membrane, particularly when eustachian tube function is normal and there is minimal middle ear inflammation (Meyerhoff et al, 1983). In a recent study in which the chinchilla was used as an animal model, it was found that a single intra-tympanic application of a commercial preparation containing neomycin, polymyxin B, and propylene glycol consistently produced total destruction of all cochlear hair cells and severe vestibular damage (Wright and Meyerhoff, 1984).

It now seems clear that laboratory rodents are very highly susceptible to the effects of toxic materials placed in the tympanic cavity and therefore do not represent ideal animal models. This vulnerability can be explained, at least in part, by the thinness and wide exposure of the round window membrane in these animals. In other species, such as the baboon, which has a thicker, more protected round window membrane, the inner ear is less severely affected following middle ear application of ototopical preparations. However, significant ototoxicity has been observed in the primate model, especially in the basal cochlear turn, where total loss of inner and outer hair-cells occurs after a single application of otic drops to the tympanic cavity (Wright et al, 1987).

In spite of the frequent clinical use of ototopical preparations, there have been relatively few reports of hearing loss or vestibular disturbance in patients treated with them (Murphy, 1970; Dumas et al, 1980; Nomura, 1984; LeLiever, 1985; Lind and Kristiansen, 1986). This may in part be due to the fact that the human inner ear is better protected from the influence of toxic substances in the middle ear cavity. In humans, the round window membrane is situated within a well-developed niche, which in many cases is covered by a "false" membrane of cuboidal epithelium. The human round window membrane is also much thicker than in most animal species (averaging 65 microns in thickness versus about 20 microns in the baboon) and it has a more densely structured intermediate layer, providing a more effective physical barrier. It must also be remembered that when topical preparations are employed in patients with tympanic membrane perforation, they usually have middle effusions and inflammatory changes of the middle ear mucosa that serve to limit access of the toxic agents to the round window membrane. Under such conditions, the round window membrane also tends to thicken and become less permeable. Several clinical investigators have in fact noted that the risk of sensorineural hearing loss in association with topical antibiotic therapy appears to be higher in patients who do not have active middle ear disease.

It may also be that the part played by ototopical preparations in sensorineural hearing loss has been underestimated, since high-frequency acuity is most likely to be affected, and clinical audiologic evaluations rarely include testing in the frequency range above 4 kHz. Thus, damage to the basal portion of the organ of Corti adjacent to the round window membrane would not be disclosed by conventional audiometric methods. Furthermore, several authors have suggested that the sensorineural hearing loss reported in association with chronic otitis media may, in some cases, be due to drugs used to treat the condition rather than to the disease itself.

In addition to inner ear toxicity, many of the constituents of ototopical preparations have been shown to produce significant inflammatory effects in the middle ear cavity, including mucosal hyperplasia, granulation tissue formation, and osteoneogenesis (Parker and James, 1978; Anderson et al, 1984; Wright et al, 1984). Middle ear tissue damage and inflammation provoked by administration of topical agents have also been found to result in the development of cholesteatoma in experimental animals (Wright et al, 1985). Among the agents used in topical preparations that contribute to middle ear irritation, propylene glycol appears to be one of the more important offenders. Even though this chemical solvent does not appear to be highly toxic to the inner ear in moderate doses, it has been shown to produce severe inflammatory and fibrotic

changes when allowed to contact directly the mucosal lining of the middle ear (Vernon et al, 1978; Morizono et al, 1980).

Thus, in view of the currently available evidence, it seems clear that topical preparations must be utilized with considerable care. The practicing physician must recognize the toxic potential of ototopical agents and judiciously tailor his or her treatment so as to decrease the likelihood of complications associated with their use.

Miscellaneous Ototoxic Agents

The literature is replete with reports of hearing loss and vestibular disturbance due to miscellaneous therapeutic agents, industrial chemicals, and heavy metals. To a considerable extent these ototoxic effects have occurred within the more general context of neurologic toxicity.

Oil of *Chenopodium ambrosioides v. anthelminticum* (American wormwood or Jerusalem oak) has a long history of use for intestinal nematodes including hookworm and ascaris. The active constituent is the organic peroxide ascaridole (1,4-peroxido-p-methene-2), which has a narrow therapeutic range. Severe intoxication with headache, central nervous system depression, coma, and death may occur. Inner ear symptoms include vertigo, ataxia, tinnitus, and deafness (Brown, 1878; North, 1880; Roth, 1918).

Interest in the ototoxic effects of arsenicals stems from their former use in the treatment of lues and trypanosomiasis. Since sensorineural hearing loss may result from lues alone, it has been difficult to separate the arsenical effect. Ototoxic effects with atoxyl (sodium arsenilate) are said to be rare among thousands of Africans treated for trypanosomiasis (Kopke, 1922) although eye symptoms are common, including optic neuritis and blindness. A single case of hearing loss and tinnitus along with blindness was reported in a patient treated with atoxyl for lichen planus (Bornemann, 1905). Another single case report concerned injections of iron arsenic that produced unilateral deafness with some gradual return of function after termination of the drug (Rosenwasser, 1932). Deafness and vestibular disturbances are rare in cases of industrial poisoning with inorganic arsenic, but hearing loss was documented in children exposed to environmental arsenic produced by burning coal with a high arsenic content (Bencko, 1977).

Propranolol, a beta-blocker used extensively for treatment of hypertension, has been associated with tinnitus and mild hearing loss. The antiarrhythmic quinidine, which is related to quinine, has been observed to produce similar symptoms (Quick, 1980). Three patients being treated with bromocriptine for hepatic encephalopathy developed bilateral sensorineural hearing loss which improved in all three with reduction of the dosage. Vasoconstriction of small cochlear blood vessels has been proposed as a possible cause of this reversible ototoxicity (Lanthier et al, 1984). In addition, pentobarbital, hexadine, mandelamine, mefenamic acid, and equine tetanus antitoxin have all been cited as potential ototoxins.

Unfortunately, many of the potentially ototoxic agents now in clinical use have no adequate non-ototoxic substitute. Therefore when such agents must be utilized, baseline

audiometric and vestibular testing should be obtained whenever possible. Periodic testing should be continued in high-risk groups, as defined by renal impairment, preexisting hearing loss, concurrent use of other ototoxic drugs, treatment for longer than 10 days, age over 65, elevated peak and trough serum levels of ototoxic drugs, and development of cochleo-vestibular symptoms during therapy. Finally, the only reliable method to minimize ototoxicity is to prevent serum drug levels from reaching such a concentration that the drugs enter the endolymph and perilymph and remain long enough to cause cochlear or vestibular injury.