

Chapter 165: Effects of Toxic Agents

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For at least two major reasons physicians need to be familiar with auditory and vestibular toxicity caused by drugs. The first is the recognition that a specific hearing loss or vestibular symptom complex is a direct consequence of an ototoxic drug. This information is important because it can (1) alter future drug therapy, especially of drugs with known ototoxic potential; (2) have obvious medico-legal consequences; (3) influence a decision on whether or not to use a cochlear implant device; and (4) provide comfort and allay anxiety because of the knowledge that there is specific cause for a patient's symptoms. The second principle benefit of having a knowledge of ototoxicity is the possible elimination or reduction of the clinical auditory and vestibular toxic effects when ototoxic drugs must be used. Patient monitoring to identify toxic effects at the earliest possible time may result in dosage reduction or a change to a nontoxic or less toxic drug, with continuation of the desired therapeutic effects and without further ototoxic side effects.

This chapter discusses current knowledge concerning ototoxic medications.

Aminoglycosides

Pharmacokinetics and biochemistry

Pharmacokinetics and the biochemical characteristics of all aminoglycoside antibiotics are similar. Because only about 3% of an orally administered dose is absorbed from the gastrointestinal tract, these drugs usually are administered parenterally. Tissue concentrations of aminoglycosides are usually about one-third serum concentrations. Penetration of aminoglycosides across the blood-brain barrier is negligible, except in neonates. Therefore when central nervous system complications of otogenic infections caused by susceptible organisms are treated with aminoglycosides, therapy will be inadequate unless the drugs are administered intrathecally (Matz et al, 1981). Previous literature has suggested that aminoglycosides are not metabolized (Sande and Mandell, 1990). However, recent experiments have suggested that an ototoxic metabolite may be formed (Huang and Schacht, 1990).

Aminoglycosides are excreted almost exclusively by glomerular filtration (Lerner and Matz, 1980), and therefore concentrations in the urine may reach levels that are more than 10 times those in the serum. Impaired renal function reduces the rate of excretion and may lead to sufficient accumulation of an aminoglycoside in the blood and inner ear tissues to cause ototoxicity, nephrotoxicity, or both. Doses therefore are adjusted downward in patients with decreased renal function. The exact mechanism for inner ear loss due to ototoxic drugs is probably best understood for the aminoglycoside antibiotics. Henley and Schacht (1988) dispute the concept of perilymph accumulation of aminoglycoside antibiotics as a cause of toxicity. They state that aminoglycoside antibiotics do not accumulate in the perilymph nor do the perilymph concentrations correlate with the development of toxicity in experimental animals. They report that the ratio of gentamicin in inner ear tissues is significantly lower when compared to plasma levels. These findings were similar to those reported by Lerner et al (1981). The biochemical molecular basis of the aminoglycoside toxicity has been well

elucidated by Williams et al (1987). Their study showed evidence of a multistep mechanism of toxicity. The initial action involves binding of the aminoglycoside to the outer plasma cell membrane. This binding effect is reversible and is antagonized by the divalent cations calcium and magnesium. The next step of toxicity may be energy-dependent uptake into the cell. Once inside the cell the aminoglycoside antibiotics interfere with a number of intracellular processes such as synthesis of the polyphosphoinositides. This is also true in humans. Ototoxicity is more probably related to a more complex pharmacokinetic function such as "area under the curve", which is approximated by determining the peak and trough levels of the aminoglycoside antibiotics. In studies on animals Beaubien et al (1989) found no relationship between ototoxicity and plasma level. Rather the total dose or area under the curve was a much better predictor of amikacin ototoxicity. The pharmacokinetics of aminoglycosides in serum and perilymph has been investigated under various conditions, such as altered renal function. Concentrations of aminoglycosides in the inner ear can be extrapolated from concentrations of these drugs in serum, which is easily sampled. Such a model allows investigations of regimens that may reduce ototoxic potential without compromising antibacterial efficacy.

Pharmacokinetics and ototoxicity

The pharmacokinetics of aminoglycosides in relation to ototoxicity have been reviewed by Henley and Schacht (1988). They presented evidence that aminoglycosides do not accumulate in inner ear fluids. Furthermore, the ototoxic potential of aminoglycosides does not seem to be correlated with aminoglycoside concentrations in inner ear fluids. The half-life of gentamicin elimination from inner ear tissues increased significantly with chronic treatment. The delayed onset of ototoxicity (Beaubian et al, 1990) suggests that redistribution of gentamicin into susceptible cells or cellular compartments is an important function in the development of ototoxicity (Henley and Schacht, 1988). More recent studies using isolated outer hair cells have demonstrated that fluorescently tagged gentamicin binds to the base of the hair cells but the ototoxic drug is excluded from the cytoplasm (Dulon et al, 1989). No effect on the viability of outer hair cells was observed unless aminoglycosides were treated by a liver fraction to generate a toxic metabolite. Anniko et al (1982) studied isolated crista ampullares and kidney tissues of the guinea pig. They found a striking similarity between the binding of radioactively labeled gentamicin and renal and vestibular structures.

Tran Ba Huy and Deffrennes (1988a; 1988b) have reported finding high-affinity binding sites for gentamicin in the organ of Corti and the vestibular maculae. A comparison of dissociation constants revealed a fourfold greater affinity of gentamicin for the vestibule than for the cochlea, which may explain the tendency for gentamicin to cause vestibular toxicity more frequently than auditory damage. Various aminoglycosides were found to compete for a common binding site, which was mainly located at the cell surface. In nonsusceptible organs such as the liver, spleen, and heart, binding of gentamicin was low and nonspecific. No significant difference in the binding of gentamicin to tissues in the cochlear apex compared to the base was found to account for the predilection for damage to occur in the basal turn initially (Tran Ba huy and Defrennes, 1990).

A revolutionary finding was recently reported by Huang and Schacht (1990). They reported that a cytotoxic metabolite of aminoglycosides caused the death of isolated guinea pig outer hair cells whereas nonmetabolized aminoglycosides had no effect on cell viability.

This may explain why ototoxicity associated with aminoglycoside antibiotics is delayed for days or weeks (Beaubian et al, 1990) despite early peak drug levels in cochlear tissues (Tran Ba Huy et al, 1986).

Another potential target for aminoglycosides is the enzyme ornithine decarboxylase. Both the kidney and cochlear enzyme were found to be inhibited by neomycin (Henley et al, 1987, 1988). Other targets in the cochlea could include the acidic glycosaminoglycans (Govaerts et al, 1990). The glutathione pathway in the cochlea may also explain a protective role against aminoglycoside ototoxicity (Hoffman et al, 1987, 1988).

Two factors have emerged experimentally that may explain the higher aminoglycoside levels in perilymph observed in patients with impaired renal function. First, in animals with compromised renal function, prolonged treatment allows equilibration of the drug between the perilymph and serum. Second, because serum levels rise with increasing duration of treatment, the level of the aminoglycoside in perilymph would be expected to rise correspondingly. Animal studies (Huy et al, 1981) showed that (1) aminoglycosides are cleared more slowly from perilymph than from serum, and (2) a decrease in renal clearance results in a prolonged half-life of aminoglycosides in perilymph. In clinical studies Matz and Lerner (1981) found higher perilymph levels of gentamicin during longer treatment schedules in patients with renal failure. These higher drug levels in perilymph may result in ototoxicity. The ototoxic effect might be minimized if the interval between parenteral doses is long enough for clearance from perilymph, but this may decrease the therapeutic efficacy.

The exact route by which aminoglycosides reach the hair cells of the inner ear from the bloodstream is not known. From the bloodstream, the drug may enter the perilymph and pass into the endolymph, or it first may enter the endolymph and then pass into the perilymph. Other fluid compartments of the inner ear may be involved as well. Animal studies (Huy et al, 1981) have shown that (1) a direct relationship exists between the degree of aminoglycoside ototoxicity and the level of the drug reached in the perilymph after systemic administration, and (2) aminoglycosides perfused directly into the perilymph space can induce toxic effects.

The pharmacokinetics of aminoglycosides in the serum and perilymph have been investigated in human subjects (Lerner et al, 1981) under various conditions, including altered renal function. The correlation has made it possible to extrapolate concentrations of aminoglycosides in the inner ear, which is relatively inaccessible, from concentrations of these drugs in serum, which is sampled easily. Based on this knowledge, aminoglycosides can be administered in dose regimens that may reduce their ototoxic potential without compromising their antibacterial efficacy.

In nephrotoxicity caused by aminoglycosides, the proximal tubular cells of the kidney appear to be a common site of injury. In rabbit kidney studies (Brion et al, 1984), the degree of tubular reabsorption appeared to differ among the aminoglycosides, with gentamicin having the highest, dibekacin and amikacin (both derivatives of kanamycin) an intermediate, and netilmicin the lowest degree of reabsorption. Renal toxicity apparently depends primarily on the degree of transport into tubular cells and intrinsic intracellular toxicity.

The uptake of aminoglycosides into the proximal tubular cells is an active, oxygen-dependent process. The routes of uptake are not fully known, but pathways have been suggested. The primary one appears to be reabsorption from the lumen of the proximal tubular cells via the brush border (Whelton and Solez, 1982); the second is an energy-dependent uptake of aminoglycosides by the basolateral membrane of these cells. This uptake mechanism seems distinct from mechanisms for other organic bases, including positively charged amino acids (Bennett et al, 1982).

Anniko et al (1982), who studied isolated cristae ampullares in the guinea pig, have demonstrated a striking similarity between binding of radioactively labeled gentamicin to renal and vestibular structures, suggesting that the nephrotoxicity and ototoxicity of this drug may have a common basis. The authors suspect that the membrane phospholipids in both tissues serve as aminoglycoside targets. In addition, Weiner and Schacht (1981) show a good correlation between the effects of aminoglycoside drugs on cochlear microphonics and their interaction with polyphosphoinositide films in vitro.

Previous studies have suggested that energy metabolism may be the target in aminoglycoside ototoxicity (Tachibana et al, 1976) or that aminoglycosides may reduce the transport of glucose into the inner ear (Garcia-Quiroga et al, 1978). Takada et al (1983) have shown that gentamicin ototoxicity is not related to glucose uptake or utilization.

Investigations by Kroese and Van den Bercken (1982) may explain biochemical findings and observations suggesting that in certain clinical situations aminoglycoside antibiotics cause reversible ototoxicity. These studies report that low concentrations of aminoglycosides may have a dual action on sensory hair cells in the lateral line organ of *Xenopus laevis*. They appear (1) to increase the spontaneous afferent nerve activity by affecting the hair cell membrane and (2) to cause marked impairment of the mechano-electric transduction process, perhaps by interfering with the motion of the sensory hairs. Takada and Schacht (1982) also have shown the reversibility of gentamicin-induced loss of cochlear microphonics in the guinea pig by using local perfusion of calcium. This supports the hypothesis that aminoglycoside ototoxicity occurs in two stages: an initial effect, which may be a membrane effect on the phospholipids, that can be antagonized by calcium (Schacht, 1979), and a second step that is noncompetitive and irreversible. This hypothesis was further confirmed by double-labeling experiments in which gentamicin was perfused directly into the ear and lipids were labeled with radioactive phosphate and radioactive glycerol. A reduced uptake of radioactive phosphate into phospholipids was found in the organ of Corti, with no alteration in the uptake of labeled glycerol into lipids in the ear treated with gentamicin. When these effects occurred, the cochlear microphonics were reduced but the ultrastructure of the cochlear tissues was not altered. This may represent the early reversible step that calcium can antagonize. The later, irreversible step presumably would result in destruction of the vestibular system and the hair cells in the organ of Corti. The initial effect apparently is on the membrane phospholipids and may result in increased sensory cell permeability with progressive loss of function until the cell eventually dies.

Phospholipid metabolism

Neomycin has been found to inhibit basal as well as agonist-induced accumulation of inositol phosphates in rat brain synaptoneurosomes (synaptosomes with attached resealed postsynaptic contents) in a dose-dependent manner (Guiramand et al, 1990).

The role of phospholipids as a target for aminoglycoside ototoxicity has been extensively studied by Schacht and his colleagues. Recent experiments have shown the presence of a specific phospholipid in isolated outer hair cells. Gentamicin has a selective and extremely high affinity for this phospholipid (phosphatidyl inositol 4.5-biphosphate) (Zenner and Schacht, 1986). In vivo studies showed a reduced incorporation of radiolabeled phosphate into the phospholipid above in the organ of Corti and stria vascularis after neomycin administration (Orsulakova et al, 1976; Stockhorst and Schacht, 1977). Schacht proposed a molecular mechanism of aminoglycoside-induced hearing loss consisting of several sequential stages: (1) reversible binding of the aminoglycoside to the plasma membrane, which can be antagonized by calcium; (2) energy-dependent uptake of aminoglycosides with features similar to polyamine uptake mechanisms; (3) intracellular binding to phosphatidylinositol 4.-biphosphate, preventing its hydrolysis and preventing subsequent formation of the second messenger inositol triphosphate and the activation of protein kinase C. These steps have also been confirmed in isolated outer hair cells (Williams et al, 1987).

Histopathology

An early effect of vestibulotoxic compounds such as streptomycin, gentamicin, and tobramycin appears to be selective destruction of type I hair cells of the crista ampullaris. Only later are the type II hair cells destroyed, and the supporting cells tend to remain intact.

In ototoxic doses, the cochleotoxic agents (neomycin, kanamycin, amikacin, sisomycin, livomycin) appear to elicit patterns of injury to the cochlea in experimental animals that are similar to the patterns seen in human temporal bones. These compounds tend to cause selective destruction of the outer hair cells in the basal turn of the cochlea, with progression toward the apex as the dose and duration of treatment are increased (Brown and Feldman, 1978). However, studies have shown a variable pattern of inner hair cell destruction that may parallel, or occur in a gradient opposite to, the destruction of the outer hair cells. The selectivity of aminoglycosides for the destruction of outer hair cells has been questioned (Browning et al, 1982).

Light-microscopic findings in the temporal bones of experimental animals treated with kanamycin have revealed a pattern of damage that includes severe destruction of the outer hair cells of the basal turn of the cochlea, with the greatest number of missing outer hair cells noted in the first row facing the tunnel of Corti (Figs. 165-1 and 165-2). Some investigators noted apical inner hair cell injury and in rare cases the supporting cells have been reported to suffer damage (Farkashidy et al, 1963; Hawkins and Enstrom, 1964; Lundquist and Wersall, 1966). Hawkins (1959, 1973) has described damage to other structures lining the cochlear duct, including the spiral ligament, stria vascularis (vascular stripe), vestibular membrane, spiral prominence, and pericapillary tissues of the outer sulcus in animals treated with kanamycin. Other aminoglycosides tend to show similar patterns of destruction in the cochlea (Brown and Feldman, 1978; Hawkins, 1976).

Continuing damage to the sensory structures of the organ of Corti after termination of treatment (delayed ototoxicity) has been documented for dihydrostreptomycin, gentamicin, and tobramycin (Theopold, 1977). Studies have shown that stereocilia can change into giant hairs (Hawkins, 1976), balloon at their base, fuse, and form intercellular bridges (Lenoir et al, 1983) before degeneration (Theopold, 1977).

In a well-documented clinical case of gentamicin ototoxicity, Keene et al (1982) used graphic reconstruction of the organ of Corti to obtain detailed information about the effect on cochlear and vestibular structures. The stria vascularis, spiral ligament, osseous spiral lamina, cochlear duct, and Reissner's membrane were all normal. The hair cells in the apex and middle coils were normal in the cochlea of this patient, who had bilateral high-frequency sensorineural hearing loss following gentamicin injections. Outer hair cells were extensively absent in the basal turn and some loss of spiral membrane cells was noted in the basal turn. Pathologic changes were seen in the vestibular sensory neuroepithelium. The hair cells of the cristae were severely vacuolized at their bases. Sensory cells in the utricle and saccule had clubbing of the distal ends of the cilia with vacuolization of the cell bodies.

We should emphasize that hair cell damage and auditory dysfunction in patients may be asymmetric (Johnsson et al, 1981). Although extensive damage to the hair cells has been documented in cases of aminoglycoside ototoxicity, the nerve fibers in the osseous spiral lamina initially remain dense (Johnsson et al, 1981). Degeneration of neurons may occur several years after the loss of inner and outer hair cells caused by kanamycin intoxication (Kiang et al, 1976). This secondary degeneration of cochlear neurons can become so extensive that the use of a cochlear implant device for tonotropic stimulation of the distal processes of cochlear neurons in the osseous spiral lamina of the basal turn probably would fail to reach higher auditory centers (Johnsson et al, 1981). Furthermore, Nadol (1984) has pointed out that even if cochlear neurons remain in large numbers, their dysfunction and delayed degeneration may limit the potential benefits of cochlear implants. He also noted that with neomycin ototoxicity, poor speech discrimination is typical despite preservation of cochlear neurons.

A provocative study by Hinojosa and Lerner (1987) found that the temporal bones from two patients with documented hearing loss after gentamicin had essential normal organs of Corti but had a reduction of cochlear ganglion cells that was about one third lower than the number observed in the cochleas of patients with normal hearing. This raises the possibility that the spiral ganglion may be the target for ototoxicity in some patients.

Ototoxicity studies

Some comparative studies have been performed in which aminoglycosides were ranked in the order of the probability of causing ototoxicity (Brown and Feldman, 1978). Animal experiments suggest that netilmicin and dibekacin (a semi-synthetic derivative of kanamycin) may be considerably less ototoxic than the aminoglycosides currently in widespread use (gentamicin, tobramycin, kanamycin, amikacin) (Aran et al, 1982; Fermin and Igarashi, 1983; Lenoir et al, 1983; Szot et al, 1980; Wersall, 1980). They have also suggested that dibekacin is one of the least cochleotoxic aminoglycosides although its vestibular toxicity appears to be similar to that of tobramycin.

Studies on humans also have demonstrated that netilmicin appears to be less likely to cause ototoxicity than some other aminoglycosides (Tjernstrom et al, 1982).

Clinical studies

Several prospective studies (Fee, 1980; Lerner et al, 1986; Smith et al, 1980) of aminoglycoside ototoxicity have been carried out. Fee (1980) and Smith et al (1980) compared gentamicin ototoxicity to tobramycin ototoxicity and found cochlear damage in 10% to 16% and vestibular toxicity in 5% to 15% of patients.

In both studies baseline audiometric tests were carried out and weekly posttreatment audiograms were obtained. In Smith's study drug assignment was random and double-blind clinical evaluations were performed. Plasma levels of the drugs were monitored by radioenzymatic assay. Auditory loss was defined as a 15 to 20 dB neurosensory hearing loss compared to baseline, and vestibular loss was defined as a reduction of 33% or more from baseline slow-phase nystagmus seen 90 seconds after the start of caloric irrigation (Fee, 1980).

In a similar randomized blind assessment of the ototoxicity of gentamicin, netilmicin, and tobramycin, Lerner et al (1984) found rates of ototoxicity comparable to those of Fee (1980) and Smith (1980). Both auditory and vestibular tests were performed and serum levels of the drugs and renal function were monitored. Lerner et al (1983) reported on the auditory toxicity of tobramycin and netilmicin in a randomized, blinded therapeutic test. CN VIII defects occurred in 12% of the tobramycin patients and 3% of the netilmicin patients.

These studies indicate a relatively low incidence of auditory toxicity. The low incidence of netilmicin toxicity cited is of potential clinical importance.

However, recent reports suggest that the incidence of aminoglycoside ototoxicity may be exaggerated; some of the changes found on audiometric testing may actually represent test-retest variability of pure-tone audiometry (Brummett and Fox, 1989; Brummett and Morrison, 1990).

Monitoring

Concentration of aminoglycosides are monitored for two reasons: (1) to ensure adequate levels for therapy, and (2) to detect elevated or rising levels that may be associated with increased risk of ototoxicity and nephrotoxicity (Lerner and Matz, 1979). The best index of renal function is creatinine clearance, but the time required in its determination makes this test impractical for routine monitoring. In patients with constant metabolic production, serum creatinine level is a good indirect estimate of the glomerular filtration rate.

Suggested schedules for determination of serum levels are as follows (Lerner and Matz, 1979):

1. For normal renal function: Peak level is determined on the first 1 or 2 days of therapy, the trough level is determined within 1 week, and peak-and-trough levels are determined weekly thereafter. Peak levels are usually drawn 1 hour after administration and

trough levels are drawn 15 minutes before administration of the next dose.

2. For impaired but stable renal function: Peak-and-trough levels are determined within the first 1 or 2 days of therapy. Serum levels may have to be monitored daily when renal function remains unstable.

Desirable peak-and-trough levels and appropriate alterations for patients with reduced renal function are given in the Table 165-1. Because these relationships are somewhat different for each drug, the package inserts in the *Physicians' Desk Reference (PDR)* should be consulted for specific details.

It has never been established conclusively that occasional elevation of serum peak-and-trough levels result in ototoxicity.

Much has been written about risk factors; in a recent study by Moore et al (1984) bacteremia, elevated temperature, liver dysfunction, and the ratio of serum urea nitrogen to serum creatinine were risk factors associated with toxicity in prospective double-blind clinical trials of gentamicin, tobramycin, and amikacin.

A recent survey of the members of the American Otologic Society (Meyerhoff et al, 1989) showed that only 4% (3 of 79) felt that pretreatment, posttreatment, and daily monitoring of auditory thresholds of aminoglycosides was necessary. The majority of respondents (52%) preferred bi-weekly monitoring of auditory thresholds in addition to pretherapy and posttherapy measurements; 32% believed that weekly monitoring was sufficient. Routine auditory monitoring of patients taking ototoxic drugs is unnecessary unless patients fall into high-risk categories. These would include patients with impaired renal function, patients who have taken aminoglycoside antibiotics in the past, patients who have consistent elevated peak-and-trough levels for therapeutic reasons, patients with unacceptably high peak-and-trough levels during treatment, patients with past or present vestibular cochlear loss, or patients in whom a vestibular or cochlear loss may be debilitating, such as airline pilots or opera singers.

Toxicology

All potential toxicities are most likely to occur in patients with compromised renal function. The aminoglycoside antibiotics primarily affect the inner ear. Dihydrostreptomycin and kanamycin have more of an effect on the auditory system than on the vestibular system; streptomycin and gentamicin appear to exert greater effects on the vestibular system, although auditory damage does occur with their use. Any of these drugs can result in simultaneously auditory and vestibular toxicity.

Acute damage to the auditory system is usually heralded by tinnitus although ototoxic effects can occur in the absence of tinnitus. The loss of hearing that results from the use of these drugs initially affects the high frequencies but, as damage progresses, lower frequencies are also affected. Humans can hear frequencies of up to approximately 16,000 Hz, but most audiometers only test hearing capability up to 8,000 Hz. Because a patient is not aware of a hearing loss until it is a 30-dB loss that includes frequencies as low as 3,000 to 4,000 Hz, the detection of ototoxicity is further complicated. Once the ototoxicity has been detected

clinically and therapy with aminoglycosides has been discontinued, ototoxic effects cease. At least some initial shifts are reversible. Ototoxic effects that present 2 or 3 weeks after discontinuation of drug therapy are likely to be permanent (Lerner et al, 1984). Because the aminoglycoside antibiotics cross the placenta, the fetal ear is also susceptible to their ototoxic effects.

The pattern of cochlear ototoxicity has been studied in various animal models to whom large doses of an aminoglycoside antibiotics have been given. The most notable effect is the early loss of hair cells in the basal turn of the cochlea. With more severe damage, this loss extends towards the cochlear apex in an orderly fashion; the first row of outer hair cells is most susceptible, followed by the middle row of outer hair cells, and then the outermost row (Lerner and Matz, 1980). Only after most of the outer hair cells have been destroyed are changes seen in the single row of inner hair cells. Next the tunnel rods as well as the other supporting cells of the organ of Corti are destroyed. The inner hair cell damage is most severe in the apex and progresses toward the base. These types of lesions also have been seen in the temporal bones of patients who have received ototoxic doses of aminoglycoside antibiotics. Because the hair cells of the organ of Corti are end-organ transducer cells for audition, they do not regenerate when they are destroyed in mammals. Therefore when auditory damage has progressed to the point at which hair cells are killed, there is no recovery (Brummett et al, 1978).

Streptomycin and gentamicin exert their effects primarily on the vestibular portion of the inner ear. In the case of streptomycin, this selectively has been used to advantage in the treatment of bilateral active Ménière's disease or to relieve symptoms and preserve hearing in patients who have only one hearing ear (that actively fluctuates) and who also suffer from disabling vertigo (Black et al, 1988). Vertigo is a manifestation of vestibular toxicity. Symmetric loss of the vestibular function is best illustrated by a patient undergoing titrated streptomycin as treatment for bilateral Ménière's disease. This patient received a total of 30 g of streptomycin, which resulted in the reduction of the patient's sum-of-sines rotation tests responses over a period of 10 weeks. This example demonstrates the importance of broad-frequency tests of vestibular ocular function for both screening and monitoring patients with bilateral progressive loss of vestibular function caused by an ototoxic drug. Tests of this type may replace the relatively insensitive air and water caloric vestibular tests for monitoring patients for vestibular toxicity. Evaluation of the vestibulo-ocular reflex by rotational testing can, however, provide the high-frequency information that caloric tests are unable to provide (Black, 1986). Also, the recent development of the moving platform posturography test has expanded the Romberg test to permit greater sensitivity in the detection and monitoring of vestibular-dependent ototoxic-induced changes in postural control.

In some cases the vestibular effects are reversible although permanent damage usually occurs. Compensation for the defect through visual and proprioceptive cues generally occurs to some extent over time. The histologic picture of drug-induced damage is similar to that for the cochlea: the most obvious effect is loss of hair cells, which, as in the cochlea, do not regenerate. Loss of hair cells is seen in the utricular and saccular macula as well as in the crista of the three semicircular canals. The reason for the selective toxicity between the vestibular and cochlear portions of the inner ear is not known.

Oscillopsia is a severe symptom of vestibular ototoxicity that can be caused by aminoglycosides. Oscillopsia is a peculiar form of disequilibrium characterized by a perception of vertical movement or "jiggling" of stationary objects. Associated findings include ataxic gait and a total absence of caloric response. Some cases may be reversible (Marra et al, 1988), whereas others can be permanent.

Cochlear toxicity has been reported following the topical application of neomycin eardrops to the round window membrane in guinea pigs (Kohonen and Tarkkanen, 1969). Hair cell damage similar to that seen after systemic administration of neomycin has been noted. In an interesting paper by Marsh and Tom (1989), five antimycotic eardrop preparations were studied. Agents studied included 25% m-cresyl acetate, 2% acetic acid, 1% clotrimazole, and 1% tolnaftate. All the agents studied were clearly ototoxic in guinea pigs. The finding of toxicity under these experimental conditions should signal the need for care in the use of suspected agents when they are used in the middle ear.

If sensorineural hearing loss occurs during the course of treatment with ototopical medications, it may not be clear whether disease or the medication caused the hearing loss. Currently streptomycin is used topically in the middle ear for the treatment of Ménière's disease, and when applied this way it will cause reduction of vestibular function. In addition, Morizono (1988) found ototoxic effects in the guinea pig from topically used gentamicin eardrops in the middle ear with concentrations as low as 0.3%. He demonstrated conclusively the ototoxicity of propylene glycol, which is one of the most commonly used carriers of drug otic solutions. It is generally understood that the ototoxic effects of these drugs can be reduced in the middle ear cavity if there is profuse ear disease with pus and thick mucosa that covers the round window. There is anecdotal evidence that indicates that topically applied ototoxic drugs may be a cause of ototoxicity and may result in severe and/or irreversible sensorineural hearing loss. Although it is difficult to correlate animal studies with topical agents used in humans, caution should be used by the clinician if these agents are to be used over a period of time.

Despite these findings, the use of eardrops containing neomycin in humans does not appear to be associated with a high risk of ototoxicity. Solutions introduced into the chronically infected middle ear of the human are probably not absorbed into the cochlea to a significant degree. Whether this is due to the oblique orientation of the human round window or to the poor penetration through the chronically infected middle ear mucosa is not certain. Despite these observations, neomycin and other eardrops should be used with caution in patients with tympanic membrane perforation. Reports in the literature document the occurrence of ototoxicity following the topical administration of neomycin to large surfaces (peritoneal cavities, wounds) by irrigation and by oral or rectal administration (Halpern and Heller, 1961). Renal failure is usually but not always a potentiating factor. Although neomycin is exceptionally ototoxic and nephrotoxic, similar use of any aminoglycoside may result in toxicity (eg, gentamicin cream on large third-degree burns or kanamycin solutions in peritoneal lavage) (Davia et al, 1970).

The role of risk factors in ototoxicity is not clear. In a few studies Lerner et al (1986) found that ototoxicity with elevated mean trough levels was associated with nephrotoxicity. In another study, univariate and multivariate analysis of risk factors of ototoxicity show only age as a predisposing factor for toxicity (Gatell et al, 1987). Factors that did not contribute

to toxicity included aminoglycoside serum levels, total aminoglycoside dosage, duration of therapy, sex, peak temperature, bacteremia, shock, liver cirrhosis, dehydration, previous ototoxic pathology, and development of renal toxicity.

Nephrotoxicity

Nephrotoxicity has been well documented with aminoglycoside usage. Initially, transient proteinuria may occur and occasionally, severe azotemia is observed. Vancomycin, furosemide, and ethacrynic acid may potentiate the nephrotoxic effects of aminoglycosides.

Other toxicities

The aminoglycosides may produce neuromuscular blockade and apnea may occur after rapid intravenous use and during peritoneal or pleural lavage and surgery under general anesthesia. These changes can be reversed with calcium or an anticholinesterase agent.

Various allergic or local hypersensitivity reactions can occur after aminoglycoside usage. The reactions can be serious, especially in patients previously sensitized to an aminoglycoside. Cross-sensitivity among members of this class is common. If allergy is present, aminopenicillins (carbenicillin, ticarcillin, piperacillin) or third-generation cephalosporins (cefotaxime, moxalactam) may be substituted.

Loop Diuretics

Pharmacokinetics and biochemistry

The loop diuretics are a group of potent synthetic drugs that act on the loop of Henle to inhibit the reabsorption of sodium, potassium, and chloride ions by a Na-K-2Cl carrier (Greger, 1985). The loop diuretics that have been tested experimentally and clinically are listed below (Gottl et al, 1985; Rybak, 1985; Rybak et al, 1991):

- Ethacrynic acid
- Furosemide
- Bumetanide
- Piretanide
- Indacrinone
- Ozolinone
- Azosemide
- Torasemide.

Although the use of ethacrynic acid is very low currently, occasionally it is used in patients who are allergic to furosemide or refractory to its diuretic effect.

Most administered furosemide is excreted in the urine. Furosemide essentially follows a three-compartment pharmacokinetic model, with an average half-life for renal elimination of 29.5 minutes (Rupp, 1974). Furosemide elimination decreases greatly in patients with advanced renal failure, in whom the half-life can be prolonged by 10 to 20 hours. Long half-lives also have been observed in patients with congestive heart failure, especially those

undergoing long-term furosemide treatment (Andreasen and Jakobsen, 1974). The plasma half-life of furosemide is approximately 45 to 92 minutes in healthy subjects (Hammarlund-Udenaes and Benet, 1989) but is prolonged to approximately 3 hours in patients with renal failure. The gastrointestinal uptake of furosemide is high; most authors have concluded that approximately 65% of an oral dose of furosemide is absorbed (Prandote and Pruitt, 1975). Plasma levels exceeding 50 mg/L frequently are associated with hearing disturbances (Quick and Hoppe, 1975; Wigand et al, 1971).

Ethacrynic acid is another potent oral diuretic; it has been used extensively in the treatment of heart failure. Ethacrynic acid inhibits glycolytic and respiratory energy production in most cells. It has been shown to facilitate the entry of gentamicin into endolymph but does not affect the kinetics of the aminoglycosides in perilymph.

Ethacrynic acid completely inhibits the transport of chloride in the ascending limb of Henle's loop and is more effective than furosemide in blocking sodium-potassium transport in sites distal to the loop. Many studies have demonstrated a biochemical interaction between aminoglycoside antibiotics and ethacrynic acid that probably allows increased penetration of the drugs into the inner ear. Boshier (1980) found that ethacrynic acid had distinctive effects on the endolymph system: it causes inhibition of potential-producing and cation-transporting processes by the stria vascularis.

The exact biochemical mechanisms of the ototoxic effects of loop diuretics have not been fully characterized. Paloheimo and Thalmann (1977) and Kusakari et al (1978) report that furosemide is a potent inhibitor of the enzyme adenylate cyclase isolated from the stria, but not sodium-potassium-adenosine triphosphatase (ATPase) at concentrations that inhibit the endocochlear potential. Studies by Marks and Schacht (1981) and Thalmann et al (1982) fail to support a role for alteration of adenylate cyclase metabolism in ototoxicity of loop diuretics. It appears clear, however, that the loop diuretics influence ion pumps in the kidney and also in the cochlear duct. Santi and Lakhani (1983) have postulated that loop diuretics block the system that transports potassium chloride out of the marginal cells of the stria vascularis. This would explain the shrinkage of the marginal cell, which may lose water if ions continue to move into the endolymph from it.

An organic acid transport uptake mechanism may play a role in the ototoxicity of furosemide. The effect of furosemide on the endocochlear potential of experimental animals was reduced by pretreatment with either probenecid, sodium salicylate, or penicillin G (Rybak and Whitworth, 1987). These are weak organic acids and may compete with other weak organic acids such as furosemide for uptake into the inner ear tissues (Rybak and Whitworth, 1987). No such protection has been demonstrated in animals pretreated with those organic acids prior to ethacrynic acid injection (Rybak et al, 1990). This suggests that the mechanism of ethacrynic acid uptake and ototoxicity may differ from that of furosemide. These findings agree with the report that the mechanism of action of ethacrynic acid on the kidney differs from that of furosemide (Greger, 1985). Furosemide also has been shown to alter active processes in the cochlea, resulting in reversible alteration of basilar membrane responses to acoustic stimuli (Rugger and Rich, 1991).

Histopathology

Morphologic studies of the inner and outer hair cells of animals treated with high doses of furosemide did not show any damage (Brown et al, 1979; Federspil and Mausen, 1973). Edema of the stria vascular has been noted in animals injected with ototoxic doses of both loop diuretics (Fig. 165-3). The edema has been demonstrated both between and within the cells (Nakai, 1971; Quick and Duvall, 1970). Some degeneration of outer hair cells at the basal turn has been reported when ethacrynic acid was administered to animals (Nakai, 1971; Quick and Duvall, 1970). No changes were observed in the cochlear nerve fibers of ganglion cells (Dilling et al, 1973; Matz and Hinojosa, 1973; Nakai, 1971; Quick and Duvall, 1970). Pike and Boshier (1980) have correlated histologic changes with alterations in the endocochlear potential in experimental animals.

A study by Arnold et al (1981) revealed morphologic effects on the temporal bones of a patient who had received a total of 5000 mg of furosemide plus 250 mg of ethacrynic acid over 5 days before dying of renal failure. The inner and outer hair cells were normal at both the light- and electron-microscopic levels, but the stria vascularis had marked cystic changes, as has been reported in animal studies (see Fig. 165-3). The dark cell areas of the vestibular system also were found to have marked cystic changes with dilation of the intracellular fluid spaces, suggesting effects on fluid transport within the inner ear.

Forge and Brown (1982) have demonstrated that the stereocilia of the outer row of outer hair cells in the guinea pig may be splayed after treatment with furosemide, and recently Comis et al (1990) have shown that the tip links between adjacent stereocilia of outer hair cells may be stretched or broken after furosemide treatment. However, at this point it is unknown whether these findings are a direct or indirect effect of furosemide.

The edema of the stria vascularis normally seen after furosemide administration is prevented by pretreatment with organic acids (Rybak and Whitworth, 1988).

Ototoxicity studies

The incidence of ototoxicity observed with ethacrynic acid therapy is unknown. Tuzel's report (1981) summarized the reported incidence of hearing loss as documented by pure-tone audiometry in 179 patients treated with bumetanide and 62 patients receiving furosemide. Among patients receiving bumetanide, only 2 (1.1%) had audiometric changes that were 15% or greater. Patients treated with furosemide has a 6.4% incidence of hearing loss. Tuzel did not report whether these hearing losses were temporary or permanent. Although most cases of loop-diuretic ototoxicity are temporary and fully reversible, some appear to be permanent (Rybak, 1982). New loop diuretics are being developed and tested in animals, and some may prove to be even less ototoxic than bumetanide.

Although most cases of loop-diuretic ototoxicity are temporary and fully reversible (Rybak, 1982; 1985) cases of permanent deafness have been reported. A recent report of permanent, profound middle- and high-frequency sensorineural hearing loss in a transplant patient receiving ethacrynic acid illustrates that deafness from loop diuretics continues to be a clinically significant problem (Rybak, 1988).

Salicylates

Pharmacokinetics and biochemistry

Orally administered salicylates are absorbed very rapidly in the gastrointestinal tract, with an apparent half-life of 6 to 15 minutes. Absorption of salicylates is influenced significantly by gastric emptying time and by the presence of food in the stomach; food may more than double the absorption half-life of aspirin. Aspirin is hydrolyzed in the body to salicylic acid, with a biologic half-life of 15 to 20 minutes (Rowland and Riegelman, 1968). Once absorbed from the serum, salicylates are distributed mainly to the extracellular water compartments (Hollister and Levy, 1965). Concentrations of the salicylates are higher in the liver and kidney than in the serum, whereas brain concentrations are usually about 10% of those in the serum. Salicylates are excreted mainly in the urine.

Salicylates quickly enter the perilymph after systemic administration. The concentration of salicylates in the perilymph reaches its maximal value about 2 hours after intraperitoneal injection in experimental animals. In chinchillas (Juhn et al, 1985) and cats (Silverstein et al, 1967), the perilymph concentration of salicylates after systemic administration was as much as one fourth to one third of the corresponding blood level.

More recent studies (Boettcher et al, 1990) recorded the serum and perilymph concentrations of salicylate after intraperitoneal injection of 450 mg/kg to chinchillas. Serum level reached a peak of 51.5 mg/dL 2 to 4 hours after injection. The relationship between serum and perilymph salicylate level was nearly linear (Boettcher et al, 1990). Jastreboff et al (1986) also reported finding a linear relationship between serum and perilymph concentration of salicylate in the rat.

Chinchillas receiving 450 mg/kg IP were found to have serum levels of salicylate of 25 to 50 mg/dL. This dose of salicylates caused an elevation of the evoked response threshold of up to 30 dB, mainly at the high frequencies (Boettcher et al, 1989a). Guinea pigs receiving salicylates at the same dosage level (450 mg/kg IP) were found to have an increased rate of spontaneous activity of neurons in the inferior colliculus, which may indicate a tinnitus-like phenomenon (Jastreboff and Sasaki, 1986).

A recent review by Boettcher and Salvi (1991) points out the differences in the results of studies of salicylate ototoxicity in various animal species. Some of the variable results are likely to be due to differences in the metabolism and disposition of salicylates in those studies (Boettcher and Salvi, 1991).

In humans, serum salicylate concentrations of 20 to 50 mg/dL result in hearing losses of up to 30 dB (Myers and Bernstein, 1965). In a recent study conducted on human volunteers, aspirin was administered at varying dosage levels. Hearing loss and tinnitus were found to occur at lower concentrations of total plasma salicylate than previously reported. The investigators found a linear relationship between hearing loss and unbound salicylate concentrations (Day et al, 1989). In comparing their charts to those of Myers and Bernstein (1965) the authors concluded that hearing loss can occur at salicylate concentrations of below 20 mg/dL. Furthermore, they concluded that there is no threshold for salicylate-induced hearing loss. Thus, even at total salicylate concentrations of 11 mg/dL the hearing loss at any

given frequency was 12 dB. Day et al (1989) also found that there was a continuous increase of tinnitus over the range of plasma salicylate concentrations from 40 to 320 mg/L.

Autoradiographic studies have shown that tritium-labeled salicylate can be detected very quickly in the blood vessels of the stria vascularis and spiral ligament (Ishii et al, 1967). Within an hour the label was found in the outer tunnel of the organ of Corti and around the outer hair cells and in Rosenthal's canal around the spiral ganglion cells. No evidence was found of salicylate accumulating in any specific cochlear structures.

Direct perfusion of sodium salicylate produces an effect similar to that of systemic injection in experimental animals, that is, a reduction in the magnitude of the action potential of the eighth cranial nerve (CN VIII) (Bobbin and Thompson, 1978). Salicylates suppressed the compound action potential at low but not at high sound intensities and also suppressed cochlear microphonics but had no effect on summing potential (Puel et al, 1990). There has been some controversy about whether salicylate effects on the cochlea are mediated by changes in prostaglandin metabolism.

Escoubet et al (1985) found that aspirin-treated guinea pigs had a significantly lower level of several prostaglandins (6-keto-PGF1a, PGF2a, and PGE2) in the lateral wall tissue. Jung et al (1988a) also reported a decrease of 6-keto-PGF1a concentration in the cochlea of chinchillas in whom aspirin had been applied to the round window. This drug application resulted in a 20- to 40-dB hearing loss. On the other hand, Puel et al (1990) perfused the guinea pig cochlea with salicylate dissolved in artificial perilymph. This resulted in a reduction of the amplitude of compound action potential elicited by low-intensity stimuli. But when the cochlea was perfused with other inhibitors of prostaglandin synthesis, the cochlear potentials were not affected. This led the authors to conclude that the ototoxic effects of salicylates on hearing are not mediated by prostaglandin effects in the cochlea.

More recent studies by Jung et al (1991) have shown that the topical application of sodium salicylate or indomethacin to the round window membrane of the chinchilla causes hearing loss of 20 to 50 dB in 1 to 2 hours as measured by brainstem audiometry and was associated with decreased concentration of 6-keto-PGF1 and elevated levels of leukotrienes. These authors found that these ototoxic effects of salicylates were mimicked by the topical application of leukotrienes to the round window membrane of the chinchilla. The application of prostaglandins to the chinchilla round window had no significant effect on hearing.

Silverstein et al (1967) proposed that salicylates inhibit certain transaminase and dehydrogenase systems and interfere with the transfer of hydrogen by diphosphopyridine nucleotide (DPN), based on their findings that malic dehydrogenase activity is reduced in labyrinthine fluids. Ishii et al (1967) have suggested that aspirin inhibits the acetylcholinesterase activity of efferent nerve endings in the organ of Corti.

Krzanowski and Matrschinsky (1971) found that in animals treated with ototoxic doses of salicylates, only the adenosine triphosphate (ATP) levels in Reissner's membrane were lowered significantly (by about 40%). The phosphocreatine content in Reissner's membrane was not changed, but the ATP and phosphocreatine content were increased in the cochlear nerve and stria vascularis, respectively.

Several investigators have attempted to identify the tissue in the cochlea that are affected by salicylates by looking for correlations with electrophysiologic studies. When they examined cochlear tissues of experimental animals by electron microscopy, even after giving massive doses of salicylates, Deer and Hunter-Duvar (1982) found no evidence of cell destruction in the stria vascularis or organ of Corti. The cochlear blood vessels appeared normal, and the stereocilia of the inner and outer hair cells were erect and not fused together. Transmission electron microscopy did not demonstrate any qualitative differences between salicylate-intoxicated and control animals in the inner hair cells, supporting cells, or stria vascularis. The outer hair cells of both experimental and control animals did have an accumulation of organelles in the subcuticular zone, but more organelles appeared to be present in the outer hair cells of treated animals. These organelles included membrane-bound vacuoles, dark-staining spheres near the Golgi apparatus, swollen mitochondria, lysosomes, and some whorls of fenestrated smooth cisternae (Hensen bodies) surrounding degraded mitochondria or collapsed vacuoles. The authors did not determine how these slight changes in the outer hair cells were correlated with hearing loss as measured by behavioral changes in the same animals.

Because of the finding that sodium salicylate selectively reduces eighth cranial nerve (CN VIII) action potential (N1) in experimental animals Mitchell et al (1973) performed ultrastructural studies on guinea pigs injected with ototoxic doses of sodium salicylate. These authors found no pathologic changes in either control or drug-treated animals when they examined a cell membrane, a nuclear membrane, mitochondria, Golgi bodies, endoplasmic reticulum, or the myelin sheath of the spiral ganglion, nor did they find changes in the exoplasm, myelin sheath, Schwann cell nucleus, or cytoplasm of auditory nerves in transverse and longitudinal section (Falk, 1974).

A comprehensive study of the effects of salicylates upon hearing was recently reported (Stypulkowski, 1990). Adult cats were intravenously administered moderately high doses (200 or 400 mg/kg) of sodium salicylate. Following drug infusion, salicylated produced an intensity-dependent reduction of the compound action potential (AP) and summing potential (SP). Endocochlear potential (EP) was unchanged while cochlear microphonic potential responses were increased independent of stimulus intensity. The author asserts that salicylates mimic the actions of efferent stimulation and that the changes observed were likely to be caused by a salicylate-mediated increase in conductance of the outer hair cells. The tinnitus, which is observed in humans and inferred from animal experiments, (Jastreboff et al, 1988; Kauer et al, 1982) may be caused by a selective temporary effect of salicylates on outer hair cells while the inner hair cells are spared; this may result in increased spontaneous firing rates in neurons innervating the inner hair cells in the high-frequency region of the cochlea (Stypulokowski, 1990).

An additional effect of salicylates on cochlear blood flow has been proposed. Hawkins (1973) reported vasoconstriction in capillaries of the suprastrial spiral ligament, the stria vascularis, and the tympanic lip and basilar membrane (inner and outer spiral vessels) in postmortem surface preparations of these tissues obtained from guinea pigs treated with sodium salicylate, quinine, and quinidine. Apparently the resulting reduced blood flow is not sufficient to cause loss of sensory cells or changes in the stria vascularis.

More recent studies have provided further support for the theory that salicylates reduce cochlear blood flow. The ototoxic effects of large doses of aspirin in the guinea pig were reduced by a sympatholytic adrenolytic compound that would antagonize vasoconstriction caused by norepinephrine-like compounds (Cazals et al, 1988). Administration of sodium salicylate to experimental animals caused hearing loss that was accompanied by a 50% reduction in the cochlear blood flow (Malotte et al, 1990) and an increase in the concentration of catecholamines and their metabolites in perilymph (Jung et al, 1990).

An experimental study of the effects of indomethacin on the inner ear morphology of guinea pigs showed somewhat questionable distention of Reissner's membrane in a few animals (Morrison and Blakely, 1978). Electron microscopy of the organ of Corti did not demonstrate any abnormalities.

Koopman et al (1982) failed to demonstrate any change in the auditory-evoked brainstem response of guinea pigs treated daily with ibuprofen in amounts comparable to therapeutic doses used for human beings. Although they collected and fixed the temporal bones following the experiment, these authors did not report the results of a histologic analysis.

Clinical studies

Studies on the temporal bones of patients with audiometrically documented salicylate-induced hearing loss have been reported (Bernstein and Weiss, 1967; DeMoura and Hayden, 1968). However, no significant cellular alterations were found at the light-microscopic level beyond those attributed to the age of the patients. Thus, although the site-of-lesion testing of the auditory system in patients suffering from salicylate-induced hearing loss strongly suggests a cochlear pattern (McCabe and Day, 1965), histopathologic studies as yet have not pinpointed which cells are altered. These apparent inconsistencies, however, corroborate the typical clinical phenomenon of reversibility of the hearing loss, thus making it likely that salicylates have some temporary metabolic effect that is not severe enough to kill sensory receptor cells or neurons.

Antineoplastic Drugs

Cisplatin

Pharmacokinetics and biochemistry

The pharmacokinetics of cisplatin were reported by Gormley et al (1979). Following a 1-hour intravenous infusion of 70 mg/m², the plasma platinum concentrations were found to have a biphasic clearance with half-life values of 23 minutes and 67 hours. Urinary measurements showed that 17% +/- 2.7% of the administered dose was excreted in the first 24 hours. Renal excretion appears to be predominantly by glomerular filtration. There is extensive and strong binding of cisplatin to serum proteins, and this cisplatin-protein complex is inactive against tumor cells. The serum levels of non-protein-bound platinum display different kinetics than those found for total platinum levels in serum. The non-protein-bound platinum in serum have a biphasic decline as did total platinum measurements, but the half-lives were much shorter. The first phase half-life was 8 minutes and the slow phase t_{1/2} was

40 to 45 minutes (Gormley et al, 1979).

It is not known whether toxic metabolites of cisplatin are formed in the inner ear or in other parts of the body such as the liver or kidney. However, the liver has been shown to rapidly convert cisplatin into nontoxic metabolites within 1 hour after dosing. The liver cytosol appears to form adducts of cisplatin with glutathione and cysteine. Cisplatin itself seems to be the most likely toxic chemical species that appears within the cells of the cortex and outer medulla of the kidney during the period following cisplatin administration when nephrotoxicity is initiated (Mistry et al, 1989).

Bagger-Sjöback et al (1980) have suggested that cisplatin inhibits the activity of adenylate cyclase in the cochlear tissues. Barron and Daigneault (1987) tested the effects of ototoxic doses of cisplatin on the lateral wall tissues of the guinea pig. Although hair cell damage was induced, no effect on the Na-K-ATPase activity in the lateral wall tissues of the cochlea was observed. This contrasts with the observation that cisplatin produced a dose-dependent inhibition of renal Na-K-ATPase in association with nephrotoxicity (Daley-Yates and McBrien, 1982). However, the inhibition of the renal enzyme appears to be an indirect effect resulting from inhibition of energy metabolism in the renal mitochondria (Brady et al, 1990).

Treatment of chinchillas with cisplatin has been reported to cause an eightfold increase in prostaglandin levels in the perilymph (6-keto-PGF_{1a}) (Jung et al, 1988b). Recent studies by Guiramand et al (1990) reported that cisplatin inhibits both basal-stimulated and agonist-stimulated accumulation of inositol phosphates in rat brain synaptoneuroosomes; the agonists are carbachol and glutamate. The synaptoneuroosomes consist of synaptosomes with attached resealed postsynaptic entities. In the presence of 6mM cisplatin, the basal inositol phosphate accumulation was 50% of the control value and the glutamate- and carbachol-induced formation of inositol phosphate was almost completely inhibited. This may explain the tendency for cisplatin to damage outer hair cells and renal tubular cells; the latter contain large amounts of phosphates. Similar disruptions of phosphoinositide metabolism were noted with aminoglycosides (Guiramand et al, 1990). Recent physiologic studies of cisplatin-deafened guinea pigs suggest a mechanism of action of cisplatin in outer hair cells that is similar to that of the aminoglycosides. Hearing loss from cisplatin was accompanied by normal values of endocochlear potential with a reduction in the sensitivity of the 2fl-f2 distortion products. The loss of sensitivity of the distortion products in dB correlated well with the loss of neural sensitivity in dB. There was also a relationship between the low-frequency cochlear microphonic potential and hearing loss in dB. These findings led to the conclusion that cisplatin causes hearing loss initially by blocking outer hair cell transduction channels (McAlpine and Johnstone, 1990) in a manner similar to that of aminoglycosides (Kroese et al, 1989), causing a reduction in hair cell receptor current and subsequent hearing loss (McAlpine and Johnstone, 1990). Because the slow contractions of the outer hair cells are probably initiated by inositol phosphate turnover in the outer hair cell, the effect of cisplatin on these cells would probably be to reduce their motility, to block their transduction channels, and eventually to destroy the cells.

The ototoxicity of cisplatin may be modulated biochemically in part by reducing substances such as glutathione in the cochlea. Cisplatin ototoxicity was reported to be reduced by treatment with sodium thiosulfate (Otto et al, 1988). Another protective agent that has been

found to reduce ototoxicity is fosfomycin, an epoxide antibiotic. Guinea pigs that were pretreated with fosfomycin were protected against hair cell loss and elevations in auditory thresholds caused by ototoxic and nephrotoxic doses of cisplatin (Ohtani et al, 1985; Schweitzer et al, 1986a).

The stria vascularis appears to be damaged only by high dose intravenous cisplatin in experimental animals, resulting in a decrease of the endocochlear potential. Multiple low-dose injections result in permanent elevations of auditory brainstem-evoked response threshold without changes in the endocochlear potential (Laurell and Engstrom, 1989). Perhaps some patients with immediate hearing loss after cisplatin suffer vascular changes and damage to the stria vascularis.

Cisplatin ototoxicity is enhanced by aminoglycosides (Schweitzer and Olson, 1984), by loop diuretics (Brummett, 1981; Komune and Snow, 1981; McAlpine and Johnstone, 1990), by aminooxyacetic acid (McAlpine and Johnstone, 1990), and by exposure to moderate or high levels of noise (85 to 100 dB SPL in chinchilla) (Boettcher et al, 1989a; Gratton et al, 1990).

Morphologic similarities exist in the pattern of cochlear damage caused by cisplatin ototoxicity and that caused by aminoglycosides. Animal experiments have shown that the outer hair cells of the basal turn of the cochlea are damaged first, with damage to the more apical cells occurring when the dosage is continued (Fleischman et al, 1975; Stadnicki et al, 1975). The first row of outer hair cells appears to suffer the greatest damage (Estrem et al, 1981; Moroso and Blair, 1983; Nakai et al, 1982; Schweitzer, 1984, 1986b). This was followed by progressive alteration of the outer hair cells, with dilatation of the parietal membrane, softening of the cuticular plate, vacuole formation, and increased numbers of lysosome-like bodies in the apical portions of the cells. Irregularity of the surface of stereocilia of both inner and outer hair cells was noted, particularly in the apical turns.

Temporal bones of patients with cisplatin-induced hearing loss have demonstrated similar findings (Wright and Schaefer, 1982). These include large, fused stereocilia; damage to the cuticular plate of the outer hair cells; and extensive loss of sensory cells in the vestibular labyrinth in specimens studied by scanning electron microscopy. In addition to noting outer hair cell degeneration in the basal turn of the cochlea (Fig. 165-4), Strauss et al (1983) reported degeneration of spiral ganglion cells and cochlear neurons in a patient with documented cisplatin ototoxicity whose vestibular neurons appeared normal.

Clinical studies

As Moros and Blair (1983) pointed out in their review of cisplatin toxicity, defining the exact incidence and severity of cisplatin-induced auditory effects is difficult because of inconsistencies in previous studies and the lack of complete data from patients too ill to cooperate for pretreatment and posttreatment audiograms.

Symptoms that strongly suggest cisplatin ototoxicity include otalgia, tinnitus, and subjective hearing loss (Reddel et al, 1982). Tinnitus has been reported in 2% to 36% of patients receiving cisplatin (Moroso and Blair, 1983). The tinnitus often is transient, lasting from a few hours up to a week after cisplatin therapy (DeConti et al, 1973). The incidence

of hearing loss among patients treated with cisplatin has been reported to be as low as 9% (Higby et al, 1974) and as high as 91% (Helson et al, 1978). The hearing loss is usually bilateral and appears first at high frequencies (6.00 and 8.000 Hz) (Helson et al, 1978; Piel et al, 1974). Progression to lower frequencies (2.000 and 4.000 Hz) may occur with continued therapy (Helson et al, 1978). The hearing loss may be asymmetric (Freeman et al, 1979) and may not appear until several days after treatment (Hayes et al, 1977). Patients may experience some degree of reversibility, but when the hearing loss is profound, it appears to be permanent (Hayes et al, 1977). Because the hearing loss tends to occur at the higher frequencies, it may not be detected without audiometry. Cochlear toxicity may be detected earlier with high-frequency audiometry (up to 20 kHz) than with conventional audiologic testing (Domenech et al, 1988; Fausti et al, 1984; Vander Hulst et al, 1988). Speech discrimination scores may be markedly reduced when cisplatin ototoxicity occurs (Piel et al, 1974; Rybak, 1981). The hearing loss may be gradual, progressive and cumulative, or may present suddenly (Chapman, 1982; Domenech et al, 1988; Guthrie and Gynter, 1985).

The critical cumulative dose of cisplatin has been reported to be 3 to 4 mg/kg body weight (Hayes et al, 1977; Lippman et al, 1973). Ototoxicity may be more pronounced after bolus injection (Kamalakar et al, 1977; Yap et al, 1978). On the other hand, the physician may minimize the ototoxic effects by using slow infusion and dividing the doses over several months (Higby et al, 1974; Kamalakar et al, 1977).

Children receiving high cumulative doses of cisplatin (above 540 mg/m²) have a high incidence of hearing loss (McHaney et al, 1983) that is cumulative (Brock et al, 1988) and dose dependent (Kluba et al, 1990). However, a plateau effect has been reported with no further deterioration of hearing at doses greater than 600 mg/m² (Skinner et al, 1990). On the other hand, a number of patients will develop more severe hearing losses in the 2 to 8 kHz range even after 1 or 2 courses of therapy. Thus, exceptions to the plateau effect exist (Myers et al, 1991). Adults with a preexisting history of otologic problems have a higher incidence of ototoxicity of cisplatin affecting both lower (1.000 to 8.000 Hz) and higher frequencies (10.000 to 18.000 Hz) (VanderHulst, 1988). Ototoxicity of cisplatin appears to be enhanced by cranial irradiation (Granowetter et al, 1983).

Standard cisplatin doses in the past were 50 mg/m². Recently cisplatin treatment regimens have been developed using higher doses of cisplatin (100 to 120 mg/m²: "high dose"; 150-225 mg/m²: "very high dose"). These increased dosage regimens have resulted in a higher incidence of hearing loss (Laurell and Jungnelius, 1990) than that observed with the lower dosage of 50 mg/m² (Laurell and Borg, 1988) as well as some different perspectives on cisplatin-induced hearing loss. In a study of 54 patients receiving "high-dose" cisplatin, Laurell and Jungnelius et al (1990) found that 81% of patients had significant threshold elevations (15 dB or more at one frequency or 10 dB or more in three frequencies). After completion of therapy, which ranged from 1 to 7 doses, 41% of the patients had significant deterioration of hearing in the speech frequency range of 0.5 to 2 kHz. As a rule of thumb, 25% of patients lost 25% of their remaining high-frequency hearing after each course. Preexisting hearing loss did not seem to predispose to ototoxicity, but advanced age increased the risk slightly. The audiogram after the first course was not predictive of further deterioration of hearing later during treatment with "high-dose" protocols. It appears that the ototoxic risk is determined more by the amount of the single dose than by the cumulative dose levels. No ototoxic effects were seen at a peak plasma concentration of less than 1

microg/L. Based on their findings, the authors recommended that patients undergoing "high-dose" cisplatin treatment have an audiogram before the start of therapy and before each of the subsequent courses. Less frequent testing was recommended for patients treated with low- and moderate-dose treatment (Laurell and Jungnelius, 1990).

Kopelman et al (1988) reported that all of their patients complained of decreased hearing after "very high-dose" cisplatin administration (150-225 mg/m²). In a recently published small series, Barr-Hamilton et al (1991) found that patients with brown eyes had significantly greater average hearing loss than those with blue eyes. The authors concluded that a greater concentration of melanin in the cochlea (which is related to eye color) caused trapping of larger amounts of cisplatin. This needs to be validated by further studies.

Studies of vestibular function in patients before and after chemotherapy with cisplatin have shown that this drug is vestibulotoxic. The vestibulotoxicity is especially likely to occur in patients with preexisting abnormalities of vestibular function; the physician should monitor such individuals closely to minimize vestibulotoxicity (Black et al, 1982).

A potentially useful screening test for cisplatin vestibulotoxicity has been reported (Kitsigianis et al, 1988). The vestibular autorotation test was used to prospectively study the horizontal vestibuloocular reflex (VOR) in nine patients with cancer who were being treated with cisplatin. The results showed decreased VOR gains at 3.1, 3.9, and 5.1 Hz, and increased phase lags at 3.1 and 3.9 Hz (Kitsigianis et al, 1988).

New series of platinum anticancer drugs have been produced and tested clinically. Carboplatin is one such derivative. The principal toxicity of carboplatin is myelosuppression, especially thrombocytopenia. Renal toxicity is not usually a problem and neurotoxicity is minimal (Kennedy et al, 1990; Schweitzer et al, 1986a).

Initial reports suggested a complete lack of ototoxicity (Calvert et al, 1982). However, studies by Van der Hulst et al (1988) and Kennedy et al (1990) have shown a significant incidence of hearing loss in carboplatin-treated patients. Of patients treated with carboplatin, 75% had measurable hearing loss in the former study, whereas 20% of patients treated with carboplatin in the latter study had measurable hearing loss. The authors in the latter study stated that no clinically significant hearing loss occurred (Kennedy et al, 1990).

A recent case report suggests that dichloromethotrexate is ototoxic. A 69-year-old patient receiving dichloromethotrexate developed profound cochleovestibular dysfunction. He initially developed unsteadiness, gait disturbance, and nausea, with a positive Romberg test, inability to perform tandem gait, and bilateral pastpointing. He also developed blurred vision with head-shaking. Electronystagmography showed direction-fixed, nonfatiguable left-beating nystagmus in the head-hanging and left head-hanging positions. Caloric testing showed a 38% canal paresis on the left. Three days later he developed fluctuating hearing, hyperacusis, and tinnitus on the left ear. He subsequently developed a progressive profound sensorineural hearing loss in the left ear (Golden et al, 1989).

Alpha-difluoromethylornithine (DFMO)

Alpha-difluoromethylornithine (DFMO) is a new antineoplastic and antiparasitic drug that inhibits the synthesis of polyamines. Early trials have revealed the unexpected side effect of sensorineural hearing loss in patients (Abeloff et al, 1984; Splinter and Romifn, 1986). The hearing loss in human trials developed after 4 to 8 weeks of therapy (Abeloff et al, 1984; Splinter and Romifn, 1986). Initially, a high-frequency hearing loss was observed, and with further treatments the middle and low frequencies were also involved. Most of the patients had significant recovery of the hearing loss 4 to 6 weeks after cessation of therapy. Animal experiments have revealed that the time course for onset and recovery were similar to that seen in humans. These studies revealed that the cochlea was the anatomic site of injury (Jansen et al, 1989; Salzer et al, 1990). DFMO inhibits cochlear ornithine decarboxylase, an effect also reported with aminoglycosides (Henley et al, 1987). Like the aminoglycosides, DFMO caused a loss of hair cells that was greatest in the basal turn of the cochlea; however, DFMO seems unique among ototoxins in causing a greater loss of inner hair cells (Salzer et al, 1990).

Erythromycin

The importance of erythromycin in the treatment of pneumonia caused by *Legionella pneumophila* and related pathogens has resulted in its increased intravenous use. Anderson et al (1952) began testing for possible adverse effects of erythromycin on the inner ear of animals in 1952. Only vestibular screening was carried out, but the investigators concluded that no damage to the eighth cranial nerve (CN VIII) could be attributed to erythromycin. Mintz et al (1973) reported the first clinical case of hearing loss related to erythromycin in 1973. At least 32 cases of bilateral, high-frequency sensorineural hearing loss have been reported in association with high-dose intravenous or oral administration of erythromycin (Schweitzer and Olson, 1984).

Patients most likely to experience hearing loss are elderly individuals with hepatic or renal failure or those with legionnaires' disease. Symptoms of ototoxicity include subjective hearing loss, "blowing" tinnitus, and occasionally, vertigo.

According to current recommendations, the dose of erythromycin does not need to be altered in the presence of renal failure (Bennett et al, 1980). However, the half-life of erythromycin appears to be prolonged in patients with renal failure, and the serum levels may be three to five times higher than predicted in patients with normal renal function (Kroboth et al, 1983). Ototoxic serum levels of erythromycin were measured in two patients: the level ranged from 63 to 78 mg/L in one patient (Taylor et al, 1981) and was 100 mg/L in the other (Kroboth et al, 1983).

Brummett and Fox (1989b) have recently reviewed evidence to support a central nervous system site for erythromycin ototoxicity. Taylor et al (1981) reported two cases of reversible hearing loss from erythromycin. One patient complained of double vision along with the hearing loss. The diplopia persisted until 1 day after cessation of antibiotic therapy and subjectively the hearing returned to normal within a few days. The second patient complained of slurred speech and was also noted to have hearing loss. These symptoms, including the hearing loss, resolved completely over 3 days, but there were no pretreatment

audiograms for comparison. The symptoms displayed by the above patients were felt to represent generalized central nervous system toxicity attributed to erythromycin. Cohen and Weitz (1981) described two cases of psychiatric complications ascribed to erythromycin. One patient complained of "confusion, fear, lack of control, abnormal thinking, and a feeling of unconsciousness or being drugged". No alteration of hearing was documented for either patient above.

Umstead and Newman (1986) reported two patients with hearing loss during erythromycin therapy. One reported short-term confusion and paranoia and the other reported hallucinations. In both cases the mental changes cleared and the hearing loss subjectively resolved.

Although the majority of cases of hearing loss associated with erythromycin therapy have been reversible, two cases of permanent auditory effects have been reported. Levin and Behrenth (1986) reported a case of permanent tinnitus lasting at least 1 year after intravenous administration of erythromycin lactobionate associated with documented hearing loss, which reverted, but the tinnitus persisted. A case of permanent hearing loss was recently reported (Dylewski, 1988). This occurred in a 73-year-old female treated with erythromycin lactobionate (500 mg IV every 6 hours) for pneumonia.

Schwartz and Maggini (1982) reported two separate episodes of reversible hearing loss in a patient given intravenous erythromycin gluceptate in two courses separated by 7 months.

Only one animal study on the ototoxicity of systemic erythromycin has been reported. Brummett et al (1984) found that erythromycin injected into guinea pigs at 125 mg/kg per hour caused a progressive effect on auditory brainstem evoked response testing (ABR). The fourth-wave latency was prolonged, then disappeared. This was followed by subsequent effects on waves III and II. No changes were found on cochlear microphonics or compound action potential. This suggests that erythromycin caused an effect on the auditory brainstem structures.

In 1984 Schweitzer and Olson published the following guidelines for the prevention of erythromycin-induced ototoxicity:

1. The daily dose of erythromycin should not exceed 1.5 g if the serum creatinine concentration is above 180 mol/L.
2. Pretreatment and posttreatment audiograms should be obtained, especially in elderly patients and patients with renal or hepatic insufficiency.
3. Caution should be exercised when erythromycin is given to patients already receiving ototoxic drugs, such as furosemide, cisplatin, or an aminoglycoside antibiotic.

Vancomycin

Vancomycin is a glycopeptide antibiotic of high molecular weight that is structurally distinct from other currently used antibiotics. Recent advances in analytic techniques have permitted the complete elucidation of the structure of this unique antibiotic (Perkins, 1982).

Vancomycin and risocetin are structurally related antibiotics that are nephrotoxic and reportedly ototoxic and cause systemic reactions as well (Waisbern et al, 1960). The recent emergence of infections with methicillin-resistant strains of *Staphylococcus aureus* has resulted in renewed interest in the use of vancomycin for such infections (Watanakunakorn, 1982). Vancomycin is also used for enterococcal endocarditis in penicillin-sensitive individuals and is used orally for *Clostridium difficile* pseudomembranous colitis. Because some methicillin-resistant staphylococcal infections have failed to respond to vancomycin, rifampin or aminoglycosides may be added to the therapeutic regimen.

The pharmacokinetics of vancomycin has been recently characterized with high-pressure chromatography (Hoagland et al, 1984) and radioimmunoassay (Cutler et al, 1984; Gross et al, 1985). Multicompartmental models have been proposed (Banner and Ray, 1984; Cutler et al, 1984). It is, therefore, important to specify from which phase of the pharmacokinetics curve a blood sample is obtained before meaningful statements that relate blood levels with toxicity can be made (Banner and Ray, 1984). Furthermore, the infusion rate can drastically affect "peak" concentrations (Banner and Ray, 1984). Usually, no significant absorption occurs after oral administration of vancomycin (Kavanagh and McCabe, 1983).

Elderly patients, even those with normal renal function, have reduced total systemic and renal clearance of vancomycin (Cutler et al, 1984). In premature infants, vancomycin has a significantly longer half-life and volume of distribution than in full-term infants. Therefore, careful monitoring of vancomycin blood levels in premature infants has been strongly recommended (Gross et al, 1985).

Hearing loss in humans has been reported at blood levels of vancomycin exceeding 45 mg/L (Snively and Hodges, 1984), but it has also been reported at blood levels of 30 mg/L (Mellor et al, 1984; Traber and Levine, 1981). Reversible tinnitus has been correlated to "peak" serum levels of the combined drugs at 40 to 50 mg/L (Alpert et al, 1984).

Vancomycin given to guinea pigs in near-lethal doses was found to be nonototoxic (Brummett et al, 1990). Therefore, although caution should be used to avoid excessive doses of vancomycin, it appears to have a very small probability of causing ototoxicity.

Vancomycin administered to 10 pregnant women for methicillin resistant *S. aureus* infections did not adversely affect either renal function or hearing in the infants born to these mothers. Vancomycin was detected in the cord blood of two patients and in the breast milk of one. It appears that vancomycin given during the second and third trimester of pregnancy does not cause transplacental sensorineural hearing loss or nephrotoxicity in the fetus (Reyes et al, 1989).

An increased incidence of nephrotoxicity has been observed in humans and animals receiving vancomycin and aminoglycosides in combination (Rybak and Boike, 1983). Potentiation of gentamicin ototoxicity by vancomycin has been recently reported in guinea pigs by Brummett et al (1990). A critical review of previously reported cases of vancomycin ototoxicity revealed that most cases of permanent ototoxicity attributed to vancomycin could be explained by concurrent treatment with aminoglycosides (Brummett and Fox, 1989b). Therefore, the probability that vancomycin is ototoxic appears rather low.

Clinical Aspects of Ototoxicity

Before the evaluation of gentamicin and cisplatin, most reports of drug ototoxicity in human beings were retrospective, that is, patients were identified only after ototoxicity appeared. The information obtained was usually based on a small number of patients who had poor renal function or who had received somewhat excessive doses of the drugs. Little information was available on the risk factors associated with ototoxicity and, most importantly, on the incidence or characteristics of the more subtle subclinical ototoxicity usually seen in clinical practice. In the last few years prospective studies of patients who received aminoglycosides or cisplatin are now available and provide considerable information about the early clinical course of ototoxicity.

Approximately 10% to 15% of patients with aminoglycoside ototoxicity have reversal of the abnormal electronystagmograms and audiograms, thus indicating reversibility of toxicity. Unilateral loss, either of the vestibular or the audiometric system, is possible in aminoglycoside ototoxicity. The usual hearing loss is in the high-frequency range, and thus we currently are testing patients who received aminoglycoside antibiotics with high-frequency audiometry to predict future low-frequency losses. Rotational vestibular testing has shown the initial and most severe vestibular effects to be in the lowest frequency range, with variable extension into higher frequencies. Although this test modality shows excellent promise for early detection of vestibular ototoxicity, it is currently expensive, not readily available, and not portable, that is, it cannot be used at the bedside. However, in ambulatory patients receiving potentially vestibulotoxic agents, testing before and during treatment can identify toxicity at its inception (Black et al, 1987; Harker and Cyr, 1991).

Bedside audiometric testing has been valuable; however, deciding how to assess the vestibular system at the patient's bedside after damage has occurred is very difficult. Positional nystagmus, previously reported as a sign of ototoxicity, is a sensitive sign of toxicity and may be the first abnormality to appear when patients are studied prospectively. Positional nystagmus as a sign of ototoxicity has to be reviewed with caution because patients who receive ototoxic drugs often also are receiving sedatives or pain medication, which can influence the presence of nystagmus. Determining vestibular toxicity by questioning the patient is extremely difficult. In many instances patients who receive ototoxic drugs are bedridden and cannot report any symptoms that can be attributed to the vestibular system. Our experience shows that most seriously ill patients who receive ototoxic drugs either cannot tolerate vestibular testing or cannot be transported to an area where vestibular testing can be recorded in a darkened room with the usual electronystagmography techniques. We are not aware of any suitable bedside testing other than the observation of positional nystagmus that can help the physician assess the vestibular system.

In most prospective studies the incidence of aminoglycoside ototoxicity is about 10%. When cisplatin ototoxicity has been determined prospectively, the rate of ototoxicity is much higher than that reported with the aminoglycosides.

Monitoring Ototoxic Drugs

It is obvious that monitoring auditory and vestibular function in all patients receiving ototoxic drugs is not practical, but all patients can be questioned regarding auditory and vestibular symptoms on daily records. Whenever possible, baseline audiometric and vestibular testing should be obtained. Ambulatory patients can be assessed with conventional and ultra-high-frequency audiometry and caloric testing with electronystagmography. Bedridden patients can be tested by any reproducible set of auditory stimuli. Usually, however, portable audiometers are available, and earphones can exclude ambient noise.

In several special patient populations, periodic testing during treatment is advisable. These high-risk groups include:

1. Patients with impaired renal function, evident either before or during therapy.
2. Patients with elevated peak-and-trough serum levels of ototoxic drugs.
3. Patients with preexisting sensorineural hearing losses, especially those resulting from ototoxic drugs.
4. Patients taking more than one ototoxic drug or those with a previous history of using ototoxic drugs.
5. Patients for whom a treatment course in excess of 14 days is planned.
6. Patients with symptoms suggestive of cochlear or vestibular toxicity that become evident during treatment.
7. Patients over the age of 65.
8. Patients taking any combination of an aminoglycoside antibiotic and a loop diuretic such as furosemide.

When early effects of ototoxicity are evident, adjustments in the dose schedules may reduce the likelihood of symptom progression. Alternately, different drugs that do not have as severe an ototoxic potential may be used.