TITLE: Ototoxicity

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[Grand Rounds Index | UTMB Otolaryngology Home Page]

Introduction

Ototoxicity is a subject that generates a great deal of interest and controversy not only for otolaryngologists, but also for general practitioners, as numerous diseases must be treated with drugs that can have cochleovestibular side effects. Ototoxicity can be defined in a number of ways, however, for the purposes of this text, it is defined as damage to the cochlea or vestibular apparatus from exposure to a chemical source.[1] The first ototoxic drugs identified were naturally occurring substances used for therapeutic purposes. The literature describes many examples of syphilitic patients treated with mercury who exhibited vertigo, deafness, tremors, and "madness".[2] Various herbs and folk medicines also had ototoxic effects, notably cinchona bark from which quinine was later derived.[2] Ototoxicity came to the forefront of clinical attention after the Waksman's discovery of streptomycin in 1944. Streptomycin was remarkably successful in treating many forms of tuberculosis, however, it was found that a substantial number of treated patients had irreversible cochlear and vestibular toxicity.[3] These early findings associated with the use of streptomycin, coupled with the ototoxicity associated with the later development of other aminoglycoside antibiotics, lead to a great deal of clinical and basic scientific research into the etiology and mechanisms of ototoxicity. Today, many well known pharmacologic agents have been shown to have toxic effects on the cochleovestibular system, including loop diuretics, salicylates, quinine, chemotherapeutic agents (e.g. cisplatin), and other antibiotics (e.g. macrolides). Basic scientists and clinicians are continually seeking to find new methods to minimize ototoxic injury while retaining the therapeutic efficacy of these agents.

Aminoglycosides

The aminoglycosides are bactericidal antibiotics that are widely used in the therapy of gram-negative bacterial infections. This group includes streptomycin, kanamycin, neomycin, amikacin, gentamicin, tobramycin, netilmicin, and sisomicin. Like most antibiotics, aminoglycosides may be administered in several ways, any of which may produce ototoxic side effects: parenterally, topically (ear drops, peritoneal lavage, ointment applied to burns), intratympanically, intrathecally, or orally (bowel preparations). These ototoxic agents enter the fluids of the inner ear by unknown mechanisms. One study suggests that toxic agents may be secreted into the perilymph by the spiral ligament or into the endolymph by the stria vascularis.[4] Agents injected into the middle ear cleft are hypothesized to enter via the round window membrane.[5]

The aminoglycosides are eliminated from the body almost entirely by glomerular filtration and have a high affinity for renal cortical tissue, thus attributing to their potential nephrotoxicity. Impaired renal function may allow excessively or persistently high plasma (and perilymph-endolymph) concentrations to develop thus increasing the risks for nephrotoxicity and ototoxicity. Regardless of their administration or elimination, all aminoglycoside antibiotics are ototoxic to varying degrees. Streptomycin, gentamicin, and sisomicin are primarily vestibulotoxic whereas amikacin, kanamycin, neomycin, and netilmicin are primarily cochleotoxic.[1] The differential ototoxicity depends somewhat on the number of free amino or methylamine groups attached to the glycoside portion of the molecule.[2] With all these drugs, however, both auditory and vestibular toxicity can occur simultaneously.

Cochlear toxicity is defined on the basis of audiometry. Most definitions of cochlear toxicity are encompassed by an increase of 10 to 20 dB in the threshold at one or sometimes two particular frequencies.[6] Kahlmeter showed in prospective, blinded studies that the rates for cochlear toxicity were similar for gentamicin, tobramycin, and amikacin (6-13%) with netilmicin resulting in the lowest incidence of cochlear toxicity (2.4%).[3] Neomycin and kanamycin are extremely toxic to the cochlea, and their use today is limited.

The risk of cochlear ototoxicity is synergistically increased in patients taking both loop diuretics and aminoglycosides concomitantly. It appears that edema of the stria vascularis caused by the diuretic allows easy access of the aminoglycosides into the endolymph. Impaired renal function is another important predictor for cochlear ototoxicity as well. Investigators are determining if once daily administration of aminoglycosides is less ototoxic than traditional multiple daily dosing schedules. By using once daily dosing, it appears that the incidence of ototoxicity is essentially unchanged, however the risk for nephrotoxicity may be reduced. Other factors have been postulated as increasing the risk of ototoxicity. These include: a prolonged treatment course (over 10 days), concomitant use of other nephrotoxic drugs, advanced age, previous aminoglycoside therapy, and a preexisting sensorineural hearing loss.[6]

Studies indicate that cochlear toxicity from aminoglycosides is less common in neonates and children than in adults. While it is difficult to obtain reliable audiometric data in children under age two, it is estimated that the incidence of cochlear ototoxicity in neonates is around 2% for each aminoglycoside with netilmicin having a slightly lower incidence of cochlear toxicity.[7]

Patterns of cochlear ototoxicity have been evaluated in many animal and human studies. The histologic evaluations showed that first outer hair cells and later inner hair cells are primarily affected by aminoglycosides. Degeneration of hair cells usually starts at the basal coil and progresses towards the apex. The stria vascularis may be involved, but loss of ganglion cells is rare.[8]

Clinically, acute cochlear toxicity is initially manifest as an increase in the threshold of the highest frequencies (4000 and 8000 Hz or higher) with progressive rise in threshold across lower frequencies. The patient may become profoundly deaf if the drug is not discontinued, however, if the drug is stopped early in the course of damage, there may be partial recovery of auditory thresholds. Typically, however, the loss is usually permanent. This damage is almost always heralded by tinnitus and the patient may initially complain of tinnitus rather than hearing impairment.[6]

Impairment of vestibular function due to aminoglycosides is less well documented. A reliable, reproducible and subjective assessment of vestibular function is much less readily available than of cochlear function. Thus, the true incidence of vestibular toxicity attributable to aminoglycosides is unknown. Not withstanding, differences in dynamic posturography can be detected in a significant number of patients receiving aminoglycosides compared with controls.[2] Studies suggest that vestibular ototoxicity occurs precipitously and without warning. Both the vestibulo-ocular and vestibulospinal systems are affected. Changes are usually detected first by dynamic posturography.[2]

Clinically, a majority of patients receive these medications because of life-threatening infections, during which long periods are spent bedridden. It is only when the patient becomes well enough that symptoms are first noted and often are incorrectly attributed to the patient's general debility. If ambulatory, the patient usually manifests dysequilibrium. They may show an ataxic gait, stumble easily, or lose their balance when turning quickly. The symptoms of severe aminoglycoside-induced vestibular toxicity most often consists of a failure to fix on the horizon with a sensation that distant objects appear to move, a term referred to as bobbing oscillopsia and reflects bilateral vestibular involvement. Compensation for the defects occurs over time through visual and proprioceptive clues.[6]

Pathologically, the initial and most extensive hair cell damage occurs in the apex of the cristae and the striolar regions of the maculae. With increasing toxicity, progression of hair cell loss extends towards the periphery of the cristae. Degeneration of the cristae ampullaris usually precedes that of the utricle and saccule. The vestibular type I hair cells are more sensitive to damage than type II hair cells. Thus, in the utricle, the type I rich striolar area is the most sensitive as is the macula sacculi.[9]

Many studies have been carried out with the aim of finding a mechanism to protect the inner ear from aminoglycosides. Iron chealators, antioxidants, glutathione, salicylates, glial cell line-derived neurotrophic factor (GDNF), and fosfomycin have shown promising results in this regard, however further studies are being performed to asses clinical utility.[10]

Prevention of the ototoxic effects of aminoglycosides is paramount. To minimize the risks of

ototoxicity, the use of netilmicin as a first line agent should be encouraged and blood levels of the antibiotic should be monitored throughout therapy. It is impractical to perform audiological or vestibular function tests on all patients taking aminoglycosides. However, such tests are important to those patients that are at "high-risk" for developing ototoxicity.[11] Such testing is warranted in patients with impaired renal function, prolonged treatment courses, concomitant usage of loop diuretics, concomitant use of other nephrotoxic drugs, advanced age, previous aminoglycoside therapy, sensorineural hearing loss, or patients in which inner ear dysfunction would create a major handicap (e.g. airline pilot, piano tuner, ballet dancer). It is recommended in these patients an audiogram be performed prior to therapy or within the first three days of therapy and weekly thereafter. Vestibular testing may include an ENG pretreatment, however patients should be tested daily with a Romberg test and a measurement of visual acuity with head movement.[6] Patients should also be questioned about symptoms such as decreased hearing, tinnitus, fullness, dysacousis, dizziness or problems of ocular fixation. In addition, patients whose serum levels exceed the recommended levels or those who develop symptoms of ototoxicity should also be tested and drug doses adjusted appropriately.

Macrolide Antibiotics

Macrolides are a group of antibiotics widely used in clinical medicine and are generally considered to be safe drugs. Erythromycin is a well-known drug in this class, which has been in use since its discovery in 1952 by McGuire.[12] It has become a popular drug to use in penicillin sensitive individuals because of the mild nature of its side effects. In addition, it is the antibiotic of choice for Legionella pneumonia and other atypical pneumonias.

The first report of erythromycin ototoxicity was by Mintz et al. in 1972.[12] They reported two cases of reversible sensorineural hearing loss after the administration of intravenous erythromycin. In each case, an audiogram revealed "bilateral perceptive deafness" (dB levels of 50-55) which returned to normal after discontinuing the drug. Since that time, over fifty case reports have confirmed a similar pattern, which seems typical of erythromycin ototoxicity. Characteristically, toxicity is apparent within three days of starting treatment and appears as hearing loss with or without tinnitus. Audiograms show all frequencies equally affected with a median threshold of 50dB. Significant recovery occurs within one day of stopping the drug and is typically complete at one month. Cases have been reported, however, in which hearing did not return to normal, typically in patients with underlying hepatic disease. While no particular route of administration is more toxic, higher doses given to those with renal or hepatic impairment puts patients at higher risk. Its incidence is unknown, however it may be underreported as most patients likely have recovered before consulting their physician.

The mechanism of action for erythromycin ototoxicity is not well understood and the site responsible for hearing loss is controversial.[13] Some authors postulate damage to the stria vascularis, which may alter cochlear ionic potentials while others argue it may be an effect on the central auditory pathways.[12]

Azithromycin and clarithromycin are newer macrolides developed to overcome some of the shortcomings of erythromycin such as intolerance and a limited antimicrobial spectrum. There is growing clinical evidence that both clarithromycin and azithromycin can cause similar reversible hearing losses.[13] A recent animal study found a reversible ototoxic effect of both drugs on transiently evoked otoacoustic emissions in guinea pigs.[13] Whether such ototoxicity will be found in humans is unknown, however with the recent release of intravenous azithromycin that allows for increased tissue penetration and higher concentrations, it is possible such cases of ototoxicity will occur.

Vancomycin

Vancomycin is generally believed to be ototoxic, according to Goodman and Gilman, the Physician's Desk Reference, and U.S. Pharmacopoeia, as well as the package insert.[14] Because of the "mycin" suffix, it is often mistaken for an aminoglycoside antibiotic. It has been postulated that because many individuals knew of the ototoxicity of neomycin and streptomycin during the time of vancomycin's discovery in the 1950's, it was generally considered to be ototoxic as well.

Many cases of vancomycin ototoxicity have been reported in the literature. It appears that some of the reported temporary changes in hearing, tinnitus, and dizziness may be associated with its use. However, many of these reported cases are flawed as other potentially ototoxic agents were used as well. In fact, in most of the cases of permanent ototoxicity attributed to vancomycin, the patients were treated either before or after therapy with an aminoglycoside antibiotic. Thus, the ototoxicity may be a result of vancomycin-induced augmentation of aminoglycoside ototoxicity. In experimental animal studies, to which large doses can be given alone, there is no convincing evidence of ototoxicity from vancomycin use.[14] In fact, one report of a patient who received six 185-mg doses of vancomycin inadvertently showed no auditory damage.[15] Thus, more studies in humans and experimental animals need to be made before definite ototoxicity can be attributable to vancomycin.

Miscellaneous Antibiotics

Case reports have found associations between other antibiotics and ototoxicity. Ampicillin, chloramphenicol, sulfonamides, and cephalosporins have been implicated in producing ototoxicity in treated patients.[16] Many of these reports are flawed, as other variables were more likely attributable to the hearing losses. Recently, Simdon implicated nucleoside analog reverse transcriptase inhibitors as causing tinnitus and hearing impairment in three patients affected with HIV.[17] While a possible correlation exists, other factors in these cases were more likely directly responsible for the apparent ototoxic effects.

Loop Diuretics

Loop diuretics are organic compounds that exert potent diuretic effects by acting on the epithelial cells in the loop of Henle of the kidney. Ethacrinic acid, furosemide, and bumetaside are the most familiar members of the loop diuretics. These drugs are used for the treatment of congestive heart failure, renal failure, hypertension, and pulmonary disorders such as bronchopulmonary

dysplasia in infants.

Unfortunately, these loop diuretics have been implicated as ototoxic in both clinical reports and experimental studies. Most commonly, there is a temporary sensorineural hearing loss, sometimes associated with subjective vestibular symptoms (vertigo), coming on within minutes of administration, associated with tinnitus and resolving spontaneously within 24 hours.[18] Some patients have been subsequently given the drug at lower doses without developing the toxicity. Other patients, however, experience a permanent hearing loss, usually those with renal failure who receive high doses. The incidence of ototoxicity of these drugs is difficult to substantiate. Rybak and others estimate an incidence of around 6-7% for each of these drugs.[18] Ethacrinic acid is postulated to be more toxic as experimental studies have shown longer recovery periods in treated animals.[18]

Pathologically, the effect of these drugs seems to be on the stria vascularis which becomes edematous which can cause changes in the ionic gradients between the perilymph and endolymph by inhibiting adenylate cyclase and G-proteins in the stria vascularis.[16]

More troublesome than the usually reversible cochlear toxicity associated with loop diuretics is the synergistic ototoxic effect the diuretics have with aminoglycosides. Animal studies indicate that following a dose of aminoglycosides, loop diuretics can cause outer hair cell loss in the cochlea up to eight hours later. The mechanism of potentiation and synergism may be as follows: the aminoglycoside interacts with the cell membranes of the inner ear, increasing their permeability. This allows easy access of the diuretic into the cells in higher concentration, causing more severe damage.[9] Interestingly, the synergism is not apparent when the diuretic is given before the aminoglycoside. The co-prescription of these drugs is, therefore, not recommended.

Salicylates and NSAIDS

Salicylates, such as aspirin, are among the most common drugs taken in the United States. Over 20 thousand tons of salicylates are consumed each year for their anti-inflammatory, antipyretic, and antithrombotic properties.[19] Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a heterogeneous group of compounds that share similar therapeutic effects as well as side effects. Since these drugs can be obtained without a prescription, they are potentially available for long-term use and abuse.[6]

The dominant ototoxic effect of salicylates appears to be the production of tinnitus as well a reversible mild to moderate symmetric sensorineural hearing loss. The hearing loss is typically mild to moderate and bilaterally symmetric. It may be flat or in the high frequencies. Recovery usually occurs 24 to 72 hours after cessation of the drug.

Studies have correlated serum salicylate levels and the development of hearing loss and tinnitus. McCabe and Dey reported temporary high frequency hearing loss with tinnitus after aspirin treatment in five normal volunteers.[20] After giving subjects 925 mg four times a day, the subjects' hearing loss progressed over a five day period from 4 dB after 24 hours to 28 dB after 4 days.

Increasing the dosage and duration of treatment increased the hearing loss. All subjects returned to baseline thresholds within 72 hours after stopping the drug. Although most reports of salicylate toxicity are reversible, a few cases of permanent hearing loss have been reported.[19] The auditory characteristics of salicylate-induced tinnitus have been described as tonal and high frequency. Pitch matching has identified involvement of tinnitus at frequencies of 7 to 9 kHz.

The onset of tinnitus has been used in the past as an initial sign of ototoxicity in rheumatoid arthritis patients. Later studies found that the onset of tinnitus should not be used as a predictor of serum salicylate level as ototoxic symptoms can be present at low blood levels.[19] The mechanism of such toxicity appears to be related to reversible biochemical or metabolic changes in the cochlea, rather than morphologic abnormalities. Examinations of patients' temporal bones who had taken large amounts of salicylates prior to death revealed normal organs of Corti with no significant hair cell loss. Some studies have found decreased cochlear blood flow after systemic application of salicylates. Other studies have pointed out a reduction in enzyme activity in the cochlea after salicylate ingestion . Overall, it appears that salicylate ototoxicity is multifactorial with decreased cochlear blood flow and biochemical abnormalities being the most culprits.[19] NSAIDs have similar dose related ototoxic effects in that they can produce a temporary loss of hearing with tinnitus.[16]

Quinine

Because the clinical manifestations are so similar, quinine and salicylates have had a historical association in the investigation of mechanisms of ototoxicity. While the use of quinine as an antimalarial drug has been decreasing in favor of less toxic semisynthetic derivatives, its use as a treatment for nocturnal leg cramps continues to rise. Thus, otolaryngologists may be increasingly called upon to treat its ototoxic effects.

The ototoxic effects attributable to quinine include vertigo, tinnitus, and a transient sensorineural hearing loss.[19] Transient hearing loss, usually a first side effect, occurs a few hours after initiation of high-dose therapy. The sensorineural hearing loss is typically reversible, bilateral, and symmetric, affecting the high frequencies first with a characteristic 4-kHz notch. Discrimination scores have been noted to drop below 30%. Perceptual tinnitus is similar to that caused by the salicylates: a high-pitched, narrow band noise or tone. Vertigo can also occur. Blood quinine levels 0.2 mg/L have been found in pilots involved in aviation crashes, which has suggested a role of quinine vestibular toxicity.[21] In addition, ENG testing has demonstrated that three of four human subjects who drank 1.6 L of tonic water daily for two weeks suffered positional abnormalities.[22] These side effects are likely secondary to decreased perfusion of the cochlea, direct damage to outer hair cells, and biochemical alterations in the cochlea.[16]

Antineoplastic Agents

Cisplatin is an anticancer drug that has been used clinically since FDA approval in 1978 as the most potent platinum chemotherapeutic agent. The major toxic side effects can be classified as GI, renal, hematological, and audiological. All are dose related and in some cases cumulative.[23]

Kovach described the ototoxicity of cisplatin as resulting in a mild threshold elevation above 4 kHz in eight of their patients.[24] DeConti reported two cases of tinnitus following cisplatin administration which persisted from several hours to one week in duration.[25] Indeed, in an assessment of the many reports of cisplatin induced hearing loss, the hearing loss is usually bilateral and symmetric. High frequencies are usually affected first, however the hearing loss may affect low frequencies as well. The elevated thresholds are generally not reversible and the effects may be cumulative with repeated doses. Age extremes, prior cranial irradiation, high individual doses, doses used in conjunction with the aminoglycosides, and high dose therapy seem to increase the risk of developing the ototoxicity.[23] The incidence varies as whether high dose or low dose regimes of administration were used. Early cancer studies describe a hearing loss in 62 % of patients, however the range for a "clinically apparent" hearing loss ranges from 0-25%. Nonetheless, Laurell found an incidence of hearing loss over 15 dB in at least one frequency in 81% of patients treated with high dose cisplatin.[25]

There has been little consensus on the nature of the primary histopathologic changes in the cisplatin-intoxicated cochlea. The most commonly reported histopathologic changes has been outer hair cell degeneration, but some reports implicate other cochlear structures such as the supporting cells of the organ of Corti and Reissner's membrane. In addition, damage to the stria vascularis has also been implicated.[16]

Many studies have been performed in attempt to protect the inner ear from cisplatin's cochleotoxic effects.[1] Studies have been performed with probenecid and found this agent to be nephro-protective but not protective against the ototoxicity. WR2721 was found to be protective in preventing hearing loss in the mid frequencies but not the higher frequencies. Diethyldithiocarbamate (DDTC) has been found ineffective in preventing ototoxicity in humans. Calcium supplementation, diuretic use, and hydration also do not offer oto-protective effects. A recent in vitro study identified L-N-acetyl-cysteine as being protective against cisplatin induced hair cell loss. Further studies are being performed on these and other agents in an attempt to find agents that may have oto-protective effects.[23]

Topical Antibiotic Drops

Topical otic preparations are commonly prescribed for the treatment otorrhea following tympanostomy tube insertion as well as for chronic suppurative otitis media with tympanic membrane perforation. It is known that with patent tympanostomy tubes or perforated tympanic membranes, these agents may enter the middle ear cleft. Once in the middle ear, these agents can contact the round window and may gain access to the membranous labyrinth. Thus, the safety of ototopical preparations remains a controversial subject because animal testing provides irrefutable evidence of significant hearing loss and hair cell death.[27]

Brummett found that polymixin B damaged hair cells in a dose dependent manner following application to the middle ear three times daily for 2 weeks.[28] Patterson and Guliuck applied

chloramphenicol to the round window and found a loss of cochlear microphonics up to 9 hours after the application.[29] Many investigators have reported dose-dependent ototoxicity of neomycin placed topically in the middle ear in guinea pigs at concentrations of 5 mg/ml or greater.[28] Webster found that 0.4mL of gentamicin was vestibulotoxic in the cat model and Parker and James found major hair cell loss after topical gentamicin use in the rodent model.[30,31] Jakob found ticarcillin to be ototoxic as well.[32] Vascodin has been shown to cause reversible middle ear inflammation and effusion but no hair cell loss or strial damage was noted in the animal model.[33] Lenarz did not find any ototoxicity after the use of ciprofloxacin topically in the middle ear.[34] Ofloxacin remains the only topical antimicrobial FDA approved for tympanostomy tube otorrhea and chronic suppurative otitis media for humans.

The otolaryngologic literature leaves no questions as to the potential ototoxicity of topical agents in experimental animals. Many authors, however, have discussed the difficulties of relating animal research to humans. Roland points out that there are significant anatomic differences.[35] The round window niche of the guinea pig are “exposed” whereas in humans it is recessed deeply within a deep bony niche and protected from middle ear fluids. He adds that the human round window membrane is 6 to 10 times thicker than the animal models and that the majority of human ears have a mucosal membrane spanning the bony margins of the round window niche, which separates the membrane itself from the middle ear space. In addition, he adds that the presence of thick mucosal edema with or without exudates may provide a significant barrier to the contact of ototopical drugs. This fact is supported by the widespread usage of these antibiotics by clinicians around the world with few side effects reported. Indeed, a study by Lundy approximated that the incidence of ototoxicity attributable to topical antimicrobials is one in ten thousand.[36]

While vestibular and cochlear damage due to the use of ototopicals is rare, it remains a real possibility for patients with an open middle ear. Therefore, physicians should be aware of this fact and prescribe these medications cautiously. Dosage and method of administration should be clearly explained to patients and they should be advised to cease treatment if any dizziness, tinnitus, or hearing loss occurs. In addition, the drops should be prescribed for as short a duration as possible to limit this potential for ototoxicity.

Conclusion

Although ototoxic medications have important places in modern medicine, they also have the capacity to do great harm and produce significant morbidity. As otolaryngologists, we play a critical role in identifying patients who are at great risk for developing ototoxicity and to identify and treat patients affected from these medications.

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