Ototoxicity: Etiology and Issues

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Several classes of drugs have been identified as having ototoxic potential: aminoglycoside antibiotics, other basic antibiotics, antimalarial drugs, loop diuretics, and salicylates. Various chemicals have also been implicated in causing ototoxicity. If certain predisposing conditions are present when a potentially ototoxic drug is administered, the risk of ototoxicity is increased. These conditions include impaired renal functioning, pregnancy, previous or concomitant treatment with another potentially ototoxic drug, inherited susceptibility to ototoxicity, and the effects of noise. Other conditions that have been associated with ototoxicity for which there is a lack of strong scientific support are age, sex, and pre-existing hearing loss. The physician's awareness of predisposing conditions combined with rational drug usage can reduce ototoxic risk to the individual.

Drugs that damage inner ear structures are labeled ototoxic. Ototoxic drugs may be vestibulotoxic, cochleotoxic, or both, depending upon the structures affected. Vestibulotoxic drugs primarily affect the vestibular portion of the inner ear, which is the mechanism responsible for postural equilibrium. Cochleotoxic drugs primarily affect the cochlear portion of the inner ear, which is the organ of hearing. There are some drugs that have a debilitating effect on both the vestibular and cochlear portions of the inner ear.[1]

Drugs are generally administered to individuals orally, locally, intravenously, or topically. Ototoxicity may result from any of these forms of administration if a high concentration of a potentially ototoxic drug accumulates in the inner ear.[2] Ototoxicity can occur at the time the drug is administered and persist after the drug has been withdrawn, or the onset of symptoms may be delayed and then appear within approximately six months after withdrawal of the drug.[3] Vestibular symptoms of ototoxicity can consist of lightheadedness, giddiness, or vertigo; if severe, cochlear symptoms can consist of tinnitus or hearing loss.[1] The hearing loss that results from ototoxicity is always sensorineural and may be bilateral or unilateral, transient or permanent, dose related or idiosyncratic.[4]

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Drugs and Chemicals Having Ototoxic Potential

Several classes of drugs have been identified as having ototoxic potential: aminoglycoside antibiotics and other basic antibiotics with similar ototoxic potential, antimalarial drugs, loop diuretics, and salicylates. In addition to these drug classes, many other drugs and chemicals have been implicated in causing ototoxicity (Table 1).[5-15]

Aminoglycoside Antibiotics

Aminoglycoside antibiotics have a common chemical structure and are used in the treatment of serious, often life-threatening infections caused by gram-negative and acid-fast bacteria. This class of drugs, along with other basic antibiotics with similar ototoxic potential, is the most dangerous of all drugs implicated in causing ototoxicity.[1] The potential of aminoglycoside antibiotics for ototoxicity is explained by their tendency to accumulate in

Table 1. Drugs and Chemicals Implicated in Causing Ototoxicity

Aminoglycoside Antibiotics	
Amikacin	Paromomycin
Gentamicin	Ribostamycin
Kanamycin	Streptomycin
Neomycin	Tobramycin
Netilmicin	
Other Basic Antibiotics	
Ampicillin	Minocycline
Capreomycin	Polymyxin B
Chloramphenicol	Tetracycline
Colistin (polymyxin E)	Vancomycin
Erythromycin	Viomycin
Framycetin	
Antimalarial Drugs	
Chloroquine phosphate	Quinine sulfate
Loop Diuretics	
Ethacrynic acid	Furosemide
Salicylates	
Aspirin	Aspirin compounds
Miscellaneous Drugs and Chemicals	
Anconite	Dextroamphetamine
Alcohol	Ergot
Aniline dyes	Formaldehyde
Antipyrine	Gelfoam
Arsenic	Hexadimethrine
Atropine	Hydrocyanide
Barbiturates	Iodine
Benzene vapors	Iodoform
Bonain's solution	Lead
Brinerdin	Mercury
Caffeine	Morphine
Camphor	Nitrobenzol
Carbon disulfide	Novocaine
Carbon monoxide	Phenylbutazone
Cassava	Potassium bromate
Chenopodium	Prednisolone
Chlorhexidine	Strychnine
Chloroform	Tobacco
Cisplatin	Valerian

the lymphatic fluids of the inner ear and remain there for a long time.[16] A complicating factor appearing to be unique to the aminoglycoside antibiotics is that symptoms of ototoxicity do not appear during the course of therapy, but rather, they appear days to weeks after the termination of therapy. Because of the delay in onset of symptoms, the physician might not be aware of any ototoxic risk to the patient and consequently will not take the appropriate action to reduce this risk.[17]

The aminoglycoside antibiotics can cause cochlear damage, vestibular damage, or both. If hearing loss occurs, it is usually bilaterally symmetrical, although cases of unilateral hearing loss have been reported.[18,19] The degree of hearing loss ranges from mild to total deafness and is usually permanent. In a study of patients receiving aminoglycoside therapy, however, Fee[20] reported that 90 percent of the ototoxic effects were unilateral and that 55 percent of the patients recovered. The onset of hearing loss is sometimes preceded by tinnitus. Vestibular symptoms are commonly experienced as lightheadedness or giddiness along with a sense of disequilibrium. The symptoms range from mild to severe and are almost always reversible.[1]

Antimalarial Drugs

The antimalarial drugs are potentially ototoxic when administered in very high daily doses and can cause tinnitus and hearing loss. The hearing loss is bilaterally symmetrical and is usually reversible[1]; however, some cases of permanent congenital deafness have been reported with the use of these drugs during pregnancy.[21]

Loop Diuretics

Loop diuretics, commonly used in the treatment of pulmonary edema or edema resulting from renal dysfunction, are potentially ototoxic when administered in high doses and can cause tinnitus and hearing loss. The hearing loss is infrequently accompanied by vestibular symptoms and is usually temporary. Although cases of permanent hearing loss have been reported in the literature, many of these patients had also concurrently received an aminoglycoside antibiotic, a drug known for its ototoxic potential.[1,22-25]

Salicylates

Salicylates are commonly prescribed for their analgesic properties. They are potentially ototoxic

when administered in very high daily doses and can cause hearing loss, usually preceded by tinnitus. The hearing loss is bilaterally symmetrical and is usually reversible with a reduction in dosage.[1] Even so, some cases of permanent hearing loss have been reported.[26,27]

Predisposing Conditions to Ototoxic Risk

The risk of ototoxicity is basically dependent upon the total dose of a potentially ototoxic drug and on the concentration of the drug in the blood serum. In many studies, however, dosage was not shown to be statistically significant when safe, therapeutic levels were used.[20,28,29] The risk of ototoxicity is greater when certain predisposing conditions are present. These conditions include impaired renal functioning, pregnancy, previous or concomitant treatment with another potentially ototoxic drug, inherited susceptibility to ototoxicity, and the effects of noise. Other conditions such as age, sex, and pre-existing hearing loss have been associated with increased ototoxic risk, although the scientific evidence is weak. The physician must be aware of the iatrogenic nature of drug-induced ototoxicity when administering a potentially ototoxic drug.[17] If any of the above conditions are present during the course of therapy, such conditions may represent contraindications to effective therapy.

Ototoxicity and Dosage

A potentially ototoxic drug reaches the inner ear by means of the circulatory system. The higher the concentration of the drug in the bloodstream, the more likely the inner ear structures will be affected. A dose larger than normally considered safe or administered longer than the recommended period serves to increase the risk of ototoxicity.[1]

Quantification of serum drug level and dosage and their relationship to ototoxicity are not well-defined.[20] In a comparative study, Stupp et al[16] showed that equivalent doses from within the group of aminoglycoside antibiotics, when administered to guinea pigs, resulted in significant differences in drug perilymph concentrations in the inner ear. Those aminoglycoside antibiotics that achieved the highest perilymph concentrations were demonstrated clinically to be the most ototoxic. The toxic effects of the aminoglycoside antibiotics may vary. The less toxic the antibiotic, the smaller the concentration of the drug in the inner ear; conversely, the more toxic the antibiotic, the greater will be its concentration in the inner ear.

Ototoxicity and Nephrotoxicity

The aminoglycoside antibiotics, in addition to being potentially ototoxic, are also potentially nephrotoxic, which further increases the risk of ototoxicity.[30] In many cases these antibiotics are used in the treatment of renal infections in which renal functioning in the patient may be impaired.[17] The aminoglycosides are excreted by glomerular filtration at a rate proportional to their concentration in the blood serum. Impaired renal functioning reduces the rate of clearance from the serum.[31] Because of the reduced capacity of the kidney to excrete these drugs, the aminoglycosides will remain in the blood serum for longer periods of time, and higher levels will accumulate in the serum and inner ear.[1]

The use of loop diuretics in the treatment of impaired renal functioning resulting from aminoglycoside therapy increases ototoxic risk by potentiating the ototoxic effects of the aminoglycosides.[32] Ethacrynic acid has been associated with cochlear toxicity when the patient was receiving concomitant treatment with an aminoglycoside antibiotic.[32-34] Furosemide has been shown to interact with the aminoglycoside kanamycin in guinea pigs, resulting in permanent cochlear damage. The ototoxic effect of this interaction was related to the dose of furosemide, which was much larger than the recommended levels considered safe for humans.[35] When administered to patients in standard doses, furosemide has not been shown to potentiate aminoglycoside ototoxicity.[36]

In actual clinical practice, the risk of aminoglycoside-induced ototoxicity related to impaired renal functioning is minimal, if it exists at all. Through periodic assessments of renal functioning and serum aminoglycoside levels, physicians can enhance therapeutic efficacy and reduce ototoxic risk by adjusting drug dosage to compensate for the impaired elimination.[20,31] When drug dosage is adjusted to maintain predefined serum levels, nephrotoxicity and ototoxicity occur independently.[28] Whenever possible, physicians should eval-

uate and follow-up patients who develop symptoms of ototoxicity related to aminoglycoside therapy.[31]

Ototoxicity and Pregnancy

The inner ear of a developing human fetus is basically complete by the end of the second trimester of pregnancy.[17] It is possible for ototoxicity to occur in utero if a potentially ototoxic drug is administered to the mother during the first six months of pregnancy. Many potentially ototoxic drugs are capable of crossing the placental barrier and damaging the developing auditory structures of the fetus.[1]

Placental transfer of the aminoglycoside antibiotics has been demonstrated in both humans and experimental animals.[37-39] In a study by Conway and Birt,[40] streptomycin was shown to cross the placental barrier, resulting in labyrinthine damage and high-frequency hearing loss in the fetus. Although streptomycin has been used in treatment during pregnancy for over 30 years, there is still some doubt as to its effects on the developing fetal ear.[17] In a study of 300 hearing-impaired preschool children, Robinson and Cambon[41] identified only two cases in which the loss could be clearly attributed to treatment of the mothers with streptomycin during pregnancy. In another study, 33 children whose mothers received streptomycin during pregnancy were followed up. A minor degree of hearing loss, possibly due to the streptomycin, was found in only two of the children.[42] When auditory changes in the newborn of mothers who were administered aminoglycoside antibiotics during pregnancy were reported, the ototoxicity occurred independently of ototoxicity in the mother.[40,41,43,44]

A case in which both mother and child became deaf after the mother had been treated with kanamycin and ethacrynic acid during the 28th week of pregnancy was reported by Jones.[45] Loop diuretics have been known to interact synergistically with aminoglycoside antibiotics, resulting in greater ototoxic and nephrotoxic risk than had these drugs been used on an individual basis.[1] The antimalarial drugs quinine and chloroquine phosphate are also capable of crossing the placental barrier. Permanent "congenital" hearing loss was reported in the newborn of mothers who were administered these drugs during pregnancy.[21]

Concomitant treatment with another potentially ototoxic drug during pregnancy can increase ototoxic risk. Also, ototoxic risk is greater if the mother experiences renal failure in addition to receiving a potentially ototoxic drug. Although it is questionable whether the developing fetal ear is more susceptible to ototoxicity than that of an adult, physicians need to be cautious when prescribing a potentially ototoxic drug during pregnancy.[31]

Ototoxicity and Synergism

An individual who has recently received or is currently taking a potentially ototoxic drug may have a greater risk of ototoxicity by synergism if administered an additional drug that is potentially ototoxic. The loop diuretics can interact synergistically with all of the aminoglycoside antibiotics.[17] The combined effects of ethacrynic acid and streptomycin have been shown to cause severe hearing loss in uremic patients.[11] Synergistic interactions have also occurred between loop diuretics and the various nonaminoglycoside antibiotics such as viomycin, polymyxin B, capreomycin, and fortimicin.[46] Even the antimalarial drugs have been shown to interact synergistically with other potentially ototoxic drugs. Nilges and Northern[47] reported a case of kanamycin ototoxicity resulting from synergism in a cochlea primed three weeks earlier with antimalarial drugs.

Ototoxicity and Genetic Predisposition

Although it is difficult to predict the effects of any drug on a given individual, one factor that possibly may render an individual more susceptible to ototoxicity is genetic predisposition. Some families were found to be highly susceptible to the effects of the aminoglycoside antibiotic streptomycin.[48,49] However, according to Brummett,[17] there is no evidence that genetic factors play a significant role in ototoxic susceptibility to the aminoglycosides.

Ototoxicity and Noise

Experimental studies on laboratory animals have shown that the aminoglycoside antibiotics kanamycin and neomycin can potentiate noise-induced cochlear damage. The nature of potentiation is in the form of increased cochlear susceptibil-

ity to damage from low-frequency, high-frequency, and impulse noise.[50] There is also evidence that noise exposure may predispose an individual to ototoxicity and that acoustic and drug-induced damage may be additive.[51] However, Davidson et al[52] did not find an additive effect in a study of children 4 to 10 years of age who received kanamycin while premature, and thus exposed to incubator noise.

The interaction of the aminoglycoside antibiotics with noise has broad implications. Many patients who spend some time in an intensive care unit (ICU) receive aminoglycoside antibiotics as part of their treatment. In the ICU these patients are often in close proximity to noisy medical equipment.[20] Such patients may have an increased risk of auditory damage, as studies have shown that hospital noise levels can exceed the maximum of 70 dB on the A-scale of a noise-level meter.[53]

Ototoxicity and Age

The age of an individual has been associated with increased ototoxic risk as it relates to renal function status. According to Weinstein and Dalton,[54] age is a strong determinant of how a drug will behave in a given individual. Renal function is relatively poor in premature infants and in full-term infants under three months of age. Renal function also tends to decline with advanced age. Axline and Simon[55] reported that high serum concentrations of kanamycin, streptomycin, and neomycin were maintained for longer periods of time in premature infants. With increased postnatal age, glomerular filtration increased with a corresponding decrease in serum half-life. Axline and Simon attributed the prolongation of these drugs in the serum to immature renal function. Elfving et al[56] reported one suspected case of severe permanent hearing loss with slight vestibular dysfunction in a 2-year-old girl treated with gentamicin in the newborn period. Finegold et al[57] reported a higher incidence of renal damage in older patients from the drug kanamycin. Renal toxicity was of concern to these authors in that it predisposed a patient to eighth nerve damage. Based upon the clinical evidence, age is an important factor to be considered in determining the appropriate dose of a drug and timing of administration based upon blood serum levels and rate and degree of excretion.[54,55]

Antibiotics should be administered in smaller doses to premature and young infants. When renal functioning reaches maturity, larger doses are required for the effective treatment of infections. With increasing age, accompanied by a gradual decline in renal functioning, the dose should be reduced.[54]

Ototoxicity and Sex

Currently only one research study has linked sex with risk of ototoxicity. Differential susceptibility to ototoxicity on the basis of sex was reported by Barza et al[29] in a comparative study of netilmicin and amikacin toxicity in 90 adults with a variety of serious gram-negative infections. Interestingly, a significant association was found between male sex and ototoxicity. The results of this study imply that male patients may be more susceptible to the ototoxic effects of the aminoglycoside antibiotics netilmicin and amikacin. Since no other study has shown an association between sex and ototoxicity, the findings must be interpreted with caution.

Ototoxicity and Pre-existing Hearing Loss

At present there is no scientific evidence linking pre-existing hearing loss with ototoxicity, although an individual with a pre-existing loss may be more susceptible to ototoxicity than an individual with normal auditory functioning. Research in this area has focused largely on noise-induced cochlear damage.[1] Reasonable precautions should be taken when administering a potentially ototoxic drug to an individual who has a hearing loss.

Conclusions

There are many drugs in use that have ototoxic potential. The risk of ototoxicity is even greater if certain predisposing conditions are present when a potentially ototoxic drug is administered. The physician's awareness of these predisposing conditions can serve to reduce ototoxic risk to the individual. There is a generally accepted adage in the medical profession that "it is better to be deaf or dizzy than to be dead." If potentially ototoxic drugs are to be used in treatment, rational drug usage by the physician is recommended to minimize ototoxic risk.[20]

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