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Ototoxicity

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What is it?

Ototoxicity is, quite simply, ear poisoning (*oto* = ear, *toxicity* = poisoning), which results from exposure to drugs or chemicals that damage the inner ear or the vestibulo-cochlear nerve (the nerve sending balance and hearing information from the inner ear to the brain). Because the inner ear is involved in both hearing and balance, ototoxicity can result in disturbances of either or both of these senses. The parts of the brain that receive hearing and balance information from the inner ear can also be affected by poison, but this is not technically considered ototoxicity and won't be covered in this information sheet. (Poisoning of the brain is classified as *neurotoxicity*).

The occurrence and degree of inner ear poisoning depends upon the drug involved as well as other factors such as heredity. Ototoxicity can be temporary or permanent. The effect of certain drugs is often temporary, while other drugs typically produce permanent changes to the ear. Some drugs can cause either temporary or permanent problems. It is important to note here that the broad majority of people who experience ototoxicity have a temporary or reversible form that does not result in a major or long-term disruption in their lives.

With *cochleotoxicity*, hearing loss or the start or worsening of tinnitus (ringing in the ears) can occur through damage to the cochlea (the hearing apparatus) or the cochlear branch of the vestibulo-cochlear nerve. *Vestibular ototoxicity* or *vestibulotoxicity* are terms used to describe ototoxicity that affects the balance organs or the vestibular branch of the vestibulo-cochlear nerve.

It is important to note that no drug is known to cause Ménière's disease, benign paroxysmal positional vertigo, or any other vestibular disorder causing fluctuating function.

How common is ototoxicity?

No one knows how many people suffer from ototoxicity each year or the percentage of vestibular disorders caused by ototoxicity. What is known is that when permanent and extensive ototoxicity occurs, the effects can take a terrible toll on a person's ability to function.

What substances can cause ototoxicity?

Scientific studies are required to confirm whether a drug is ototoxic. Unfortunately, such research often involves years of study. When assessing the safety of a drug prior to releasing it on the market, the U.S. Food and Drug Administration does not require testing of inner ear function or examination of the inner ear structures. This is one reason it is almost impossible to say with confidence how many and which drugs cause ototoxicity and how many or which people are affected by it.

Problems with a particular drug are usually only discovered after enough people have suffered the consequences and when physicians or other health care professionals can see a probable connection between the symptoms or problems and a drug. This was the case with aspirin and quinine centuries ago, with the antibiotic streptomycin in the 1940s, and more recently with some anti-cancer drugs. Since then, scientific studies have shown that these drugs cause ototoxicity in animals and people. Other, newer drugs have been implicated as ototoxic as well, but solid scientific proof is often lacking.

Many chemicals have ototoxic potential, including over-the-counter drugs, prescription medications, and environmental chemicals. The information below includes substances thought to cause ototoxicity. The discussion is incomplete because of the limited research thus far. *Note:* if you are taking drugs on the advice of your physician, DO NOT STOP TAKING THEM just because you see them listed here! Speak with your doctor about your concerns to determine the best choice in your own unique situation.

Aspirin and quinine Aspirin (acetylsalicylic acid, ASA) and quinine are well known to cause temporary ototoxicity resulting in tinnitus. They may also reduce hearing, particularly when given at high doses. Quinine products can also temporarily reduce balance ability. Once aspirin or quinine is stopped, the ototoxicity generally disappears. Some quinine products include:

- chloroquine
- quinidine
- quinine (including Q-vel)
- tonic water

Loop diuretics are a specific family of "water pills" that is known to occasionally cause temporary ototoxicity. These drugs cause ringing in the ears or decreased hearing that reverses when the drug is stopped.

An increased probability of ototoxicity is thought to occur with loop diuretics when they are administered during the same time period that an aminoglycoside antibiotic (see next section) is given. The loop diuretics include:

- bumetanide (Bumex)
- ethacrynic acid (Edecrin)
- furosemide (Lasix)

- torsemide (Demadex)

Note: Hydrochlorothiazide (HCTZ) and Maxide—diuretics commonly prescribed to people with Ménière's disease or other forms of endolymphatic hydrops—are not loop diuretics.

Aminoglycoside antibiotics All members of the aminoglycoside antibiotic family are well known for their potential to cause permanent ototoxicity if they enter the inner ear. Some of these drugs are more likely to cause hearing loss; others are more likely to cause vestibular loss. Others can cause either problem.

A higher risk for aminoglycoside-antibiotic induced ototoxicity occurs when a person receives concurrent ototoxic drugs (such as a loop diuretic or another antibiotic—vancomycin), has insufficient kidney function or is receiving a drug that causes insufficient kidney function, or has a genetic vulnerability.

The risk of ototoxicity also increases with an increasing amount of the drug that enters the blood stream, the longer the drug is in the body, and the duration of time the drug is taken.

Aminoglycoside antibiotics can enter the inner ear through the blood system or via diffusion from the middle ear into the inner ear. They enter the blood stream in largest amounts when given intravenously (by IV) and in the least amounts by pill. Inhaled drugs also enter the blood stream; an example of this is the use of inhaled tobramycin for long-term treatment of cystic fibrosis.

Can ear drops containing aminoglycosides be problematic? If they find their way into the middle ear in large enough quantities, such ear drops can diffuse into the inner ear and cause damage. Physicians do not agree about how often and under what circumstances this occurs. Many papers in medical journals address this argument.

Members of the aminoglycoside family include:

amikacin	netilmicin
dihydrostreptomycin	ribostamycin
gentamicin	streptomycin
kanamycin	tobramycin
neomycin	

Anti-neoplastics (anti-cancer drugs) Anti-cancer drugs work by killing cancer cells. Unfortunately some can also damage or kill cells elsewhere in the body, including the ears. Cisplatin is well known to cause massive and permanent hearing loss. Carboplatin is also known to be ototoxic.

- carboplatin
- cisplatin

Environmental chemicals have long been implicated in ototoxicity. Little research has been done to substantiate their precise effect on ears, but most are associated with hearing disturbances that may be permanent. In addition, mercury

has also been linked to permanent balance problems.

butyl nitrite	mercury
carbon disulfide	styrene
carbon monoxide	tin
hexane	toluene
lead	trichloroethylene
manganese	xylene

What damage occurs?

Two areas can be damaged or destroyed through ototoxicity: the hair cells within the inner ear, and the vestibulo-cochlear nerve that links the inner ear to the brain. When damage occurs, any degree and combination of hearing loss and balance disruption are possible depending upon the part(s) affected.

Hair cells are located in both the cochlea and the vestibular areas of the inner ear. They are composed of a cell body with a hair-like attachment. When these "hairs" are normally bent with sound vibrations or movement, they send electrical signals to the brain about hearing or balance function. In ototoxicity, these hairs can be damaged to the point that they no longer stand up, thus reducing the auditory and/or balance signals sent to the brain.

What are the symptoms?

Cochleotoxicity symptoms range from mild tinnitus to total hearing loss, depending upon each person and the form and level of exposure to the ototoxin. They can include one-sided or two-sided hearing loss and constant or fluctuating tinnitus.

Vestibulotoxicity symptoms range from mild imbalance to total incapacitation. Symptoms of a vestibular or balance function loss depend upon the degree of damage, if the damage occurred rapidly or slowly, if it's one-sided or two-sided, and how long ago the damage occurred. A slow one-sided loss might not produce any symptoms, while a rapid loss could produce enough vertigo, vomiting, and nystagmus (eye jerking), to keep a person in bed for days. Most of the time, the symptoms slowly pass, allowing a person to return to normal activities.

A two-sided loss in vestibulotoxicity typically causes headache, a feeling of ear fullness, imbalance to the point of being unable to walk, and a bouncing and blurring of vision (oscillopsia) rather than intense vertigo, vomiting, and nystagmus. It also tends to produce inability to tolerate head movement, a wide-based gait (walking with the legs farther apart than usual), difficulty walking in the dark, unsteadiness or the sensation of unsteadiness, lightheadedness, and significant fatigue. If the damage is severe, symptoms such as oscillopsia and problems with walking in the dark or with the eyes closed will not diminish with time.

How is ototoxicity diagnosed?

The diagnosis is based upon the patient's history, symptoms, and test results. There is no specific test for ototoxicity; this makes a positive history for ototoxin exposure crucial to the diagnosis. Some of the tests that may be used to

determine how much hearing or balance function have been lost involve the vestibular autorotation test (VAT), vestibulo-ocular reflex testing equipment (VORTEQ), electronystagmography (ENG), computerized dynamic posturography (CDP), rotary chair (SHAT), head-shaking, electrocochleography (EcoG), auditory brainstem response (ABR), otoacoustic emissions, pure tone audiometry, speech discrimination, and most other tests often used to identify and quantify inner ear problems.

What is the treatment?

At present there are no treatments that can reverse the damage. Currently available treatments focus on reducing the effects of the damage and rehabilitating function. Specifically, individuals with hearing loss may be helped with hearing aids; those with profound bilateral (two-sided) hearing loss have been shown to benefit from cochlear implants. In fact, many early recipients of cochlear implants were victims of ototoxicity.

When a loss of balance function has occurred, physical therapy can help the brain become accustomed to the altered balance signals coming from the inner ear. Physical therapy can also assist an individual in developing other ways to maintain balance such as emphasizing the use of vision and proprioception—the sensation felt by the soles of the feet, the ankles, knees, and hips— and structuring a program of general physical conditioning and exercises designed to strengthen and tone muscles.

Long-term goals

The major long-term goals include continuing with conditioning activities to improve balance function, protecting the other systems involved with maintaining balance, and preventing further ototoxic damage.

Protection of other components of balance—vision and proprioception—is essential. Good vision is crucial in the face of a severe vestibular loss. Yearly ophthalmological examinations that include a glaucoma check should become routine. Use of ultraviolet (UV) eye protection in the sun and eye protection in the wind (such as goggles or sunglasses) should be considered.

Protecting proprioception involves taking precautions such as avoiding walking barefooted on any surface that could injure or damage the soles (such as on a macadam road surface), not wearing clothing that restricts circulation to the legs and feet (such as a tight girdle), and taking off excess body weight that can cause knee and hip difficulties.

Avoidance of ototoxic substances is also very important because individuals who have suffered from ototoxicity have a higher likelihood of experiencing it again, if exposed. A medic alert tag might be helpful for warning health care professionals about the need to avoid prescribing ototoxic medications unless

needed to save your life. Such tags might also serve to flag an existing reduction in balance and/or hearing function.

Prevention

Limit using drugs to those that are absolutely needed and follow the instructions carefully for those medications that are prescribed for you. If possible, avoid taking multiple types of ototoxic drugs (aspirin, quinine, loop diuretics, and aminoglycosides). When using airborne chemicals that are potentially ototoxic, good ventilation should be used. Open the windows, turn on a fan, and refrain from using the chemical for any longer than necessary. Stay well hydrated.

A look at the future

Ongoing related research addresses prevention and treatment. Chemicals are being evaluated for their ability to prevent ototoxicity and that might be prescribed in tandem with ototoxic drugs in the future. Investigators are also studying methods of hair-cell and nerve-cell regeneration. In the distant future, it may be possible to stimulate the ear into growing replacement hair cells and to repair damaged nerve fibers.

Endnote

Most of the drugs listed in this document appear because strong evidence exists to show that they cause or probably cause ototoxicity. This evidence includes at least one of the following criteria:

- Large numbers of isolated reports about particular drugs or chemicals
- Experiments showing that animals develop ototoxicity when given the drug
- Multiple post-mortem studies that demonstrate changes in the ear that are linked to ototoxins in people who took certain drugs and who subsequently developed symptoms of ototoxicity. (Such ear damage can only be observed after death, when the ears can be examined fully.) An example of this type of research is Zheng et al, 2001.
- Scientific reports about groups of people tested before (if possible), during, and after their use of a drug, some of whom were found to develop ototoxicity while taking the drug. An example of this type research is Black et al, 2001.

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