Chapter 42
Complications to Medical Treatment

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Keypoints

1. When medical treatment is blamed, tinnitus may be harder to treat.
2. Adverse consequences are better accepted and more easily managed if the patient had been well informed before treatment started and had acknowledged and accepted the risk.
3. Ear syringing, suctioning, instrumentation, local anaesthetic injection, grommet insertion, dental treatment, hyperbaric oxygen therapy, and ototoxic ear drops are all relatively minor procedures that may be blamed for tinnitus.
4. Major ear operations may cause hearing loss and tinnitus.
5. Ototoxic drugs can cause hearing loss and tinnitus after administration systemically, intrathecally, or topically to extensive wounds or burns as well as from use as eardrops.
6. Onset of tinnitus is occasionally blamed on radiation therapy, noisy organ imaging, medical equipment accidents, neck manipulation, and general anesthetic.
7. Tinnitus can be triggered by procedures on any region of the body when there have been excessive pain and associated anxiety, fear, and anger.
8. The medical treatments most commonly accused of causing tinnitus are treatments with drugs. Usually, the tinnitus improves when the drug is withdrawn, provided there is no permanent damage to the cochlea or powerful associated factors.
9. Drugs with proven ototoxicity and that also cause tinnitus include aminoglycoside antibiotics, antineoplastic drugs, anti-inflammatory drugs, loop diuretics, antimalarials, and others. The ototoxicity may be synergistic with other agents that damage the inner ear.
10. Drugs that are not usually considered ototoxic but are sometimes blamed for causing tinnitus include lidocaine, anticonvulsants, antidepressants, cannabinoids, antihypertensives, beta-adrenergic blocking agents, opioids (buprenorphine), caffeine, and antihistamines. At times, drugs from within most of these groups are also credited with ameliorating tinnitus.

Keywords Tinnitus • Complication of treatment • Medical misadventure • Ototoxicity • Pathogenesis • Drug-induced tinnitus • Therapy-induced tinnitus

Introduction

Many differing medical treatments are thought by patients to have triggered the onset of their tinnitus [1]. Indeed, there are a variety of mechanisms and pathways by which this may occur. Medical treatment can result in reduced or abnormal stimulation through the auditory, somatosensory, vestibular, and other sensory pathways. Activity in central pathways can be affected directly. Unwanted effects of medical treatment may be temporary, but are associated with tinnitus that may persist once triggered. Medical treatment of almost any type throughout the entire body may be blamed as the trigger for the onset of tinnitus when that treatment has had powerful emotional associations and was accompanied by severe pain.

Tinnitus tends to be worse, and its management more difficult when the onset has been associated with fear or anger. Unfortunately, for the patient and therapist, when

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A.R. Møller et al. (eds.), *Textbook of Tinnitus*,
DOI 10.1007/978-1-60761-145-5_42,

the onset of tinnitus is perceived as being a complication of medical treatment, it is usually associated with anger and often with fear and anxiety as well. This can make management difficult. The main exception is when the possibility of tinnitus developing had been anticipated, clearly explained, and then accepted by the patient as an acceptable trade-off for life-saving treatment.

As clinicians, we may sometimes support a patient's claim for compensation for tinnitus, which the patient attributes to medical treatment they had received. More often, however, many of us encourage our patients to disassociate their tinnitus from such emotionally charged triggers. We justify doing so on the basis that the association is unproven and that dwelling on it makes the tinnitus more intrusive and harder to manage. A review of the tinnitus literature shows that we seldom investigate a suspected relationship between the onset of tinnitus and a medical treatment, let alone report it.

This chapter is an opportunity to review not only the situations in which tinnitus is acknowledged as a complication of medical treatment but also situations that have been largely ignored in scientific literature as causes of tinnitus but which, in one author's experience, occasionally are. The editors are to be congratulated for making it possible to consider all situations in which tinnitus may be a complication of medical treatment. Some of the sections in Part 1 of this chapter express unsubstantiated opinions acquired from Dr. Goodey's otological practice and his discussions with colleagues. They are presented as a challenge to other colleagues for wider consideration. Part 2 of this chapter focuses entirely on drug therapy as a trigger for tinnitus. It discusses drugs with proven ototoxicity, and some of those that are sometimes accused of causing tinnitus but not considered ototoxic. Part 2 draws heavily on Dr Enrico's extensive knowledge and experience as a neuropharmacologist.

Part 1: Procedural Treatments that May Cause Tinnitus

Minor Procedures in and Around the Ear

Often, procedures that clean the ear of wax and/or debris also reduce or eliminate any associated tinnitus. However, such procedures may occasionally trigger or aggravate tinnitus. Other procedures in the region may also trigger or aggravate tinnitus. Quite often (but not always), temporomandibular joint dysfunction may be aggravated by the same procedures and consequently aggravate the associated tinnitus.

Ear Syringing

Ear syringing is only occasionally mentioned in journal articles as a trigger for the onset of tinnitus [1–3]. However, it is frequently acknowledged as a trigger by patient support groups [4]. Even some of the more professional support groups find it necessary to produce brochures on the association [5, 6]. Mostly, they provide balanced and generally reassuring information. In such brochures, the triggering of tinnitus is sometimes attributed to ear syringing, but only when it is "poorly performed." Many otologists who deal with patients troubled by tinnitus accept that some of these patients appropriately attribute the onset of their tinnitus to ear syringing.

Occasionally, syringing-induced tinnitus has been associated with rupture of the tympanic membrane (especially if it was already weakened). Rarely, there has been major trauma to the middle ear, and inner ear as well, especially if a carelessly attached nozzle came off with the pressure used. However, more commonly, any trauma attributable to syringing has been relatively minor and confined to the ear canal. The symptoms associated with the onset of tinnitus induced by syringing are pain and vertigo. Tinnitus is especially likely to have occurred and persisted if the doctor or nurse continued to syringe an ear after the patient had wanted them to stop.

Syringing should be avoided in those with a weakened or perforated eardrum (or a grommet) or with an infected ear canal. The water used must be at body temperature. The nozzle must be firmly attached; it should have a smooth and rounded tip; and it must be directed at the posterior canal wall. If pain or vertigo is induced, the procedure must be stopped immediately.

Ear Suctioning

Ear suctioning is often recommended as a safe alternative to syringing, and it usually is. It is the treatment of choice when there is a perforation or a grommet

(tympanostomy tube) or if the ear canal is infected. However, noise levels at the suction tip are sometimes loud enough to be distressing to the patient and to trigger tinnitus [7–11], even when there is no measurable change in the audiogram.

Tinnitus is more likely to be triggered if the suction noise is excessively loud because of the material being aspirated. In this context, noise levels of 96 dB have been measured at the suction tip [12]. Tinnitus is more likely to be triggered if the commencement of the suction noise is abrupt and unexpected. If inner ear damage occurs, it may be a direct consequence of noise energy. Alternatively, inner ear damage could result from violent contraction of the stapedius muscle, as can be caused by a sound blast. However, Dr. Goodey is not aware of any patients in whom the annular ligament has been damaged and a perilymphatic fistula caused as a result of suctioning.

During suctioning, tinnitus and hyperacusis may occur and persist without any persisting change in hearing. In some of these, the situation may be identical with "acoustic shock disorder" described in comparable situations [13, 14]. Associated symptoms may include acute ear pain, muffled hearing, a feeling of fullness and numbness, and occasionally vertigo. Tinnitus and hyperacusis may persist when all the other symptoms have settled. In such situations, the inner ear may have been protected by the intermittent pattern and relatively short duration. A possible mechanism for the symptoms could be contraction of tensor tympani.

Suctioning of a mastoidectomy cavity or through a perforation often triggers vertigo. Occasionally, this is followed by persistent tinnitus, especially if suctioning was continued after the patient had become distressed.

A wise microscopist will always ask in advance whether the patient is intolerant to loud noise and always instruct their patient to tell the microscopist to stop if the suction noise is hurtful, causes vertigo, or is otherwise distressing.

Cleaning the Ear Canal Skin with Instruments

Cleaning of the ear canal with instruments often causes superficial ulceration and sometimes lacerations. Occasionally, a patient reports that it triggered their tinnitus. Ear canal injury or infection may also lead to chronic changes in the ear canal skin, which may then have a continuing effect on tinnitus.

Trauma Affecting the Middle Ear and/or Inner Ear

Clumsy instrumentation or failure to adjust to sudden head movement (such as during removal of a foreign body) can cause damage not only to the ear canal skin but also to the tympanic membrane, ossicular chain, and – through inadvertent manipulation of the chain – the inner ear. Tinnitus may result even without measurable hearing loss.

Injection of Local Anaesthetic

Injection of local anaesthetic into the ear canal in preparation for a minor surgical procedure occasionally triggers severe vertigo, which may last several hours and be extremely distressing for the patient. Accompanying tinnitus is insignificant because the vertigo is so distressing. Occasionally, tinnitus persists after nausea and vertigo have subsided. The development of effective topical anaesthetics has largely eliminated the need for injections of local anaesthetic into the ear canal for minor procedures [15].

Insertion of a Grommet

Quite commonly, insertion of a grommet to relieve Eustachian tube dysfunction or a middle ear effusion also reduces any associated tinnitus. Occasionally, however, insertion of a grommet may trigger or aggravate tinnitus, even when there has been no reaction to the local anaesthetic used and when the procedure has been gentle. In this situation, the tinnitus usually subsides or reverts to its previous level if the grommet is removed promptly, and the resulting hole was covered with a rice paper patch.

Dental Treatment

Case history questionnaires may include dental treatment as an item associated with the onset of tinnitus [16]. In Dr. Goodey's experience, dental treatment can

be a potent trigger or aggravator of tinnitus. The tinnitus tends to be more severely affected on the side of the dental treatment and occurs more often if the procedure has been prolonged and painful and associated with anxiety. There is usually associated temporomandibular joint dysfunction and sometimes aggravation of chronic neck problems as well. However, dental treatment as a trigger for tinnitus receives little or no attention in the literature, whereas dental disorders as triggers for tinnitus do receive some attention [17–19].

Without associated factors, noise from dental drilling is seldom, if ever, loud enough and prolonged enough to cause hearing loss and tinnitus in patients. However, dentists and their assistants may occasionally suffer occupational noise-induced hearing loss and tinnitus after many years of exposure [20]. Malfunction of an air drill can cause a sudden and unexpected loud blast of noise and result in tinnitus and associated symptoms described as the acoustic shock disorder in the section "Ear suctioning" of this chapter.

Barotrauma

In the context of medical treatment, barotrauma is only likely to be blamed as the trigger for tinnitus when there has been difficulty in equalizing while hyperbaric oxygen was being used as an adjunct to therapy [21]. The incidence of barotrauma as a consequence of hyperbaric oxygen therapy has been assessed and correlated with conditions being treated [22, 23]. An associated incidence of tinnitus gets little mention. Occasional patients are adamant that their tinnitus occurred or became worse during hyperbaric oxygen treatment. If equalizing problems have occurred during a previous treatment session, or are anticipated, then a mini grommet will give complete protection during subsequent treatments. When treatment in a hyperbaric chamber is required following a diving accident, then any inner ear damage can usually be attributed to the original accident and not to the treatment.

Ototoxic Ear Drops

When the eardrum is perforated or has a grommet, there is potential for ototoxic components in ear drops to cause sensorineural hearing loss and trigger tinnitus. The incidence of this occurring has been very low considering the widespread use over a large number of years [24]. However, hearing loss and tinnitus from the use of such drops do occur. The risk is probably minimized if such drops are only used when the middle ear mucosa is inflamed. A modern clinician is unwise to allow such drugs to be used in high-risk ears or once the middle ear mucosa is healthy [25]. Fluoroquinalone antibiotic drops are now available, which are proven clinically and experimentally to be nonototoxic [26–28]. Unfortunately, they tend to be much more expensive and also less well tolerated, especially by children. Nevertheless, with expert panels in the US, Canada, United Kingdom, and Australia all advocating the use of fluoroquinalones, a clinician who continues to prescribe potentially ototoxic drops has to be prepared to justify the need for these types of medications.

Major Procedures in and Around the Ear

Stapedectomy, labyrinthectomy, tympanoplasty, simple myringoplasty (especially with an overlay graft, which involves more manipulation of the malleus), mastoid surgery, vestibular nerve section, and vestibular schwannoma surgery can all trigger tinnitus. However, these have all been dealt with in the section "Complications of surgical treatment". Any resulting tinnitus is usually associated with additional sensorineural hearing loss.

As with the minor ear procedures, these more major operations only occasionally cause damage and tinnitus. More often, they reduce or relieve pre-existing hearing impairment and associated tinnitus or they have no effect on tinnitus.

Occasional Causes of Unexpected Tinnitus and Sometimes of Cochlear Hearing Loss

Radiation Therapy

Prior irradiation increases the incidence of ototoxicity, including tinnitus, during subsequent treatment with cytotoxic drugs [29]. Usually, the possibility of such life-saving treatment causing hearing loss and tinnitus will have been understood and accepted as a risk by patient. Occasionally, this is not the case, and the unexpected symptoms greatly increase the patient's distress. In the past, irradiation to reduce vascularity of a glomus tumor has caused

unexpected cochlear damage and tinnitus. Irradiation is no longer used in this context. However, the inner ear is occasionally damaged during irradiation of intracranial tumors, even when cytotoxic drugs are not used. Resultant hearing loss may be accompanied by tinnitus. In Dr. Goodey's experience, tinnitus is more likely to occur if postirradiation necrosis of the external ear canal also occurs. Presumably, this is because of the added effect of somatosensory stimulation. Subsequent care of the ear canal helps reduce the impact of the tinnitus.

Noise from Organ Imaging Equipment Especially MRI

Patients sometimes attribute their tinnitus or its increased intrusiveness to the noise associated with having an MRI [30]. Noise levels have been measured in excess of 93 dB [30] and continue throughout the relatively lengthy procedure. There is no associated increased hearing loss. Probably, anxiety, fear, and the claustrophobic environment have contributed, even though the patient has blamed the noise alone for the onset or aggravation of their tinnitus. Any patient with troublesome tinnitus should use hearing protection during an MRI.

Medical Equipment Accidents

During otologic surgery, noise levels generated by otologic drills have been measured as 82–106 dB and by suctions measured as 71–84 dB. These are considered acceptable levels. No change in postoperative bone conduction was found [31]. Others have recorded noise levels from air turbine drills of 116 dB and at suction tips of 96 dB [12]. It is widely accepted that there is a high risk of inner ear damage if a drill burr comes in contact with an intact ossicular chain or suction is applied to perilymph in the oval or round window or lateral canal fistula. A hose becoming detached from a compressed air cylinder has triggered severe hearing loss and tinnitus. Other incidents have been reported anecdotally and include a gas explosion.

Neck Manipulation

Patients regularly claim that manipulation of their neck was the trigger for their tinnitus. The resultant tinnitus can usually be modulated by neck movement suggesting proprioceptor disturbance–triggered somatosensory tinnitus. However, in some patients, neck manipulation triggered severe temporary vertigo as well as persistent tinnitus. It may be that on some occasions, neck manipulation triggers tinnitus (and sometimes vertigo) through temporary effects on the vertebral arteries. In others, radiological evidence of facet joint damage caused by manipulation has been demonstrated [32]. If a patient's neck is to be manipulated vigorously, there should be preceding organ imaging expertly read, the therapist should be experienced, and the therapist should stop immediately if untoward symptoms start to develop.

General Anaesthetic

Tinnitus may be triggered after almost any type of surgical procedure, but mostly if the procedure was under general anaesthetic and a relaxant has been used. There may be postoperative suboccipital headache as well. In these circumstances, the tinnitus can usually be modulated by the neck. Some anesthetists maintain gentle traction on the head and neck while relaxants are wearing off and claim that this reduces the incidence of postoperative headache. In Dr. Goodey's experience, this maneuver can reduce postoperative tinnitus as well. It is a wise precaution in a patient who already has troublesome tinnitus, especially if they blame it on a previous operation under general anesthesia.

Sometimes, postoperative tinnitus is associated with temporomandibular joint pain and can be modulated by the jaw. In these circumstances, difficulty with intubation may have been the mechanism.

General Reaction to Painful Procedures

In Dr. Goodey's experience, distressing and painful surgery anywhere in the body can act as the trigger for the onset of tinnitus. The resulting tinnitus may be extremely distressing and difficult to manage. This occurs most often if the pain experienced has been excessive because of complications or inadequate anesthesia, and especially when there are powerful emotional associations because of the nature of the surgery and the consequences of it.

Occasionally, there may be associated sudden hearing loss suggesting microembolism, especially after breast, orthopedic, and cardiac surgery.

Most often there is no measurable change in hearing. There may be some pre-existing hearing impairment, which may have predisposed the patient to the onset of tinnitus in response to the powerful triggering effects of pain, anxiety, fear, and anger.

Part 2: Drug Therapies, Which May Cause Tinnitus

Ototoxicity from Medical Therapy

Over 150 medications and chemicals have been reported to be potentially able to induce hearing loss and/or tinnitus, possibly by acting on both peripheral and central acoustic structures [33–35]. Drug-induced ototoxicity may be reversible or irreversible and associated with both acute and long-term administration of drugs. Among the major classes of ototoxic drugs are the aminoglycosides and other antimicrobial agents, antineoplastic drugs, anti-inflammatory drugs, loop diuretics, antimalarial drugs, and others (Table 42.1). Due to their importance in clinical practice, some ototoxic drugs are discussed in more detail below.

The pharmacological and chemical heterogeneity of drugs, which share the ability to induce hearing loss and/or tinnitus, is noteworthy. Unfortunately, research in this field is often limited by several problems, among which is the lack of a good animal model. As a consequence, the neurobiological basis of drug-induced ototoxicity is still largely unknown and may involve biochemical and physiological changes in discrete parts of the acoustic system [35]. So far, there is no evidence of a common pathway leading to drug-induced damage of acoustic structures.

Chemotherapy of Microbial Diseases

Aminoglycosides

Aminoglycosides are an important group of antibacterial drugs used primarily against Gram-negative aerobic and facultative anaerobic bacteria. Streptomycin is also effective against several tubercular and nontubercular mycobacteria, including *Mycobacterium tuberculosis*, the etiological agent of tuberculosis. Aminoglycosides are bactericidal and act by binding to the 30 S subunit of bacterial ribosomes, disrupting the elongation of the peptide chain; they may also impair translational accuracy resulting in misreading of the mRNA sequence. Aminoglycosides are poorly absorbed from the gastrointestinal tract and, therefore, are usually administered parenterally by injection or infusion. Aminoglycosides are well distributed into bodily fluids, except for the eye and the central nervous system. As their metabolism within the body is negligible, aminoglycosides are excreted unaltered by glomerular filtration (serum half-life of 2–3 h). They are also found in breast milk but, as they are not well absorbed orally, these drugs are considered compatible with use during breastfeeding [36]. Aminoglycosides are classified as an FDA pregnancy category D (positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk). Therefore, they should be used during pregnancy only when the alternatives are worse.

All aminoglycosides are able to induce both reversible and irreversible damage at cochlear, vestibular, and renal level. Nevertheless, aminoglycosides are still among the most commonly used antibiotics worldwide, mainly because of their cost effectiveness [33], but also to face the emergence of bacterial strains with advanced patterns of antimicrobial resistance [37, 38]. Aminoglycoside toxicity correlates with the total amount of drug administered and occurs in almost all patients exposed to a toxic dose. The risk of toxicity is increased if impaired renal function is allowed to cause the serum level to rise [39]. Abnormally high sensitivity to the ototoxic effects of aminoglycosides (idiosyncracy) may also be an inherited trait, and several mutations at the mitochondrial genome level have been identified [40, 41]. Cochlear and vestibular structures appear to differ in sensitivity to aminoglycosides-induced damage. Indeed, streptomycin and gentamicin are mainly toxic at the vestibular level, while amikacin, neomycin, dihydrostreptomycin, and kanamycin act primarily at the cochlear level [34, 41]. Netilmicin appears to be as effective as gentamicin, but is less ototoxic [38, 41].

Both animal and human studies show that aminoglycosides affect outer hair cells first and later the inner hair cells. Degeneration of hair cells usually starts at the basal turn and progresses toward the apex. The mechanisms of aminoglycoside-induced ototoxicity

Table 42.1 Drugs which are claimed to cause ototoxicity and/or tinnitus

	Ototoxic	Tinnitus
Drugs acting at synaptic and neuroeffector junctional sites		
β2-selective adrenergic receptor agonists		
Procaterol		+
Nonselective β adrenergic receptor antagonists		
Timolol		+
Serotonin receptor agonists		
Almotriptan		+
Eletriptan		+
Ergonovine		+
Methyl ergonovine		+
Drugs acting on the central nervous system		
Anticonvulsants		
Valproic acid	+	
Flecainide		+
Antidepressants – Tricyclic		
Desipramine		+
Amitriptyline		+
Antidepressants – SSRI		
Fluoxetine		+
Citalopram		+
Autacoids: drug therapy of inflammation		
NSAIDs		
Acetyl salicylic acid	+	+
Meclofenamic acid		+
Diclofenac		+
Ketoprofene		+
Indomethacin		+
Diflunisal		+
Acemetacine		+
Oxaprozin		
Corticosteroids		
Methylprednisolone		+
Antihistamine agents		
Chlorphenamine		+
Hydroxyzine		+
Doxylamine		+
Prometazine		+
Drugs affecting renal and cardiovascular function		
Loop diuretics		
Furosemide	+	+
Ethacrinic acid	+	+
Torasemide	+	+
Bumetanide	+	+
Inhibitors of carbonic anhydrase		
Diclofenamide		+
Antiarrhythmics		
Flecainide		+
Dihydrochinidine	+	
ACE inhibitors		
Enalapril		+
Imidapril		+
Benazepril		+

(continued)

Table 42.1 (continued)

	Ototoxic	Tinnitus
Moexipril		+
Calcium channel blockers		
Nicardipine		+
Angiotensin II receptor antagonis		
Irbesartan		+
Drugs affecting gastrointestinal function		
Sulphasalazine		+
Chemotherapy of parasitic infections		
Chloroquine	+	
Hydroxychloroquine	+	+
Mefloquine		+
Quinine		+
Sulfadoxine – pyrimethamine		+
Chemotherapy of microbial diseases		
Aminoglycosides	+	+
Macrolides		
Eritromycin	+	
Azithromycin		+
Clarithromycin		+
Quinolones		
Lomefloxacin	+	+
Moxifloxacin	+	+
Rufloxacin		+
Cinoxacin		+
Cephalosporins		
Ceftibuten		+
Cefepime		+
Lincosamides		
Lincomycin		+
Tetracyclines		
Minocycline		+
Sulfonamides		
Cotrimoxazole		+
Sulfadiazine		+
Glycopeptides		
Teicoplanin	+	+
Vancomycin	+	+
Antivirals		
Ganciclovir	+	
Lopinavir		+
Ritonavir		+
Antifungal		
Amphotericin B	+	
Griseofulvine	+	
Chemotherapy of neoplastic diseases		
Platinum compounds		
Cisplatin	+	+
Carboplatin	+	+
Oxaliplatin	+	
Immunomodulators		
Muromonab CD3	+	+
Hormones and hormone antagonists		
Bisphosphonates		
Risedronate		+

have not been fully characterized; however, several mechanisms have been proposed, including disruption of mitochondrial protein synthesis, generation of reactive oxygen species (ROS), and excitotoxicity from enhancement of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor function [39, 41].

Approaches to Protection

Due to the widespread use of these drugs, prevention of aminoglycosides-induced ototoxicity is very important. Patients should also be questioned for symptoms of tinnitus, decreased hearing, dizziness, disequilibrium, and problems of ocular fixation. Careful monitoring of serum levels together with audiological or vestibular function tests are essential components of the standard of care required to reduce the incidence of aminoglycoside ototoxicity.

Scientific research is now focused on the biological mechanisms underlying aminoglycosides-induced damage in order to develop coherent attempts at protection such as administration of antioxidants or iron chelators, interference with cell death signaling pathways, and blockade of glutamate NMDA receptor [41–44]. At present, experimental evidence shows a decrease in ototoxicity when antioxidants or iron chelators are co-administered with aminoglycosides. However, successful translation of experimental evidence to the clinic is a slow process requiring consideration of many points. Therefore, the currently more "orthodox" approach of monitoring serum drug levels and ototoxicity symptoms remains the standard of care [39, 45].

It may be impractical to monitor serum drug levels and perform audiological or vestibular function tests on all patients receiving treatment with aminoglycosides. It is essential to do so in those patients with high risk for developing ototoxicity, including those receiving prolonged treatment courses, those who have had previous aminoglycoside therapy, those with sensorineural hearing loss, or patients in whom inner ear damage would create a disproportionately major handicap. Because the incidence of ototoxicity is related to the serum aminoglycoside concentrations, it is critical to reduce the maintenance dosage of these drugs in patients with impaired renal function or who are concomitantly taking loop diuretics [46] or nephrotoxic drugs. The elderly are especially at risk from aminoglycosides, as their renal function may be significantly impaired without increase in serum creatinine.

Idiosyncratic hearing loss induced by aminoglycosides is, in theory, preventable by genetic screening to identify those at risk (e.g., individuals with the m.1555 A>G mutation). The use of such genetic screening is questioned because of the high cost of the tests. However, when the expenses of genetic screening are compared to the lifelong management of a profoundly deaf child, the cost effectiveness of genetic screening may prove very favorable [40].

Chemotherapy of Neoplastic Diseases

Platinum Compounds–Cisplatin

In theory, any drug with the capacity to destroy malignant cells should be regarded as having the potential to damage the cells of the cochlea and cause hearing loss and tinnitus. Cisplatin (*cis*-diamminedichloroplatinum) is an inorganic platinum coordination complex used alone or in combination with other anti-cancer agents. Its main application is in the medical therapy of malignancies including sarcoma, small-cell lung cancer, germ cell tumors, lymphoma, and ovarian cancer [36, 47]. Cisplatin disrupts DNA function in several ways. It inhibits DNA synthesis by the formation of DNA cross-links; it denatures the double helix and covalently binds to DNA bases interfering with replication and transcription [48, 49]. Cisplatin is administered parenterally either by the intravenous or by the intraperitoneal route. It is not metabolized but is excreted mainly by the kidney (>90%). A few studies have examined the excretion of cisplatin into human milk with contradictory results, and therefore, breastfeeding during cisplatin therapy should be considered contraindicated. Cisplatin is nephrotoxic, neurotoxic, mutagenic in bacteria, produces chromosomal aberrations in animal cells in tissue culture, and is teratogenic and embryotoxic in mice [50]. There are no adequate well-controlled studies in pregnant women [51], and Cisplatin is therefore classified as FDA pregnancy category D.

Cisplatin ototoxicity seems to be mediated by the generation of ROS in the cochlear tissue and has been shown to act on at least three major targets: the organ of Corti, the spiral ganglion cells, and the lateral wall [52]. Increased ROS and organic peroxide following

the administration of ototoxic doses of cisplatin would overwhelm the antioxidant potential of the cochlear cells, leading to calcium influx, which would activate the apoptotic pathway causing cell death [39, 52]. Several genetic variants have been associated with increased sensitivity to cisplatin-induced ototoxicity [52–54]. Research in this field is still in an early phase. However, it is conceivable that a better understanding of the genetic variants associated with cisplatin-induced ototoxicity may be an important step toward case selection and safer cisplatin treatment [53, 55, 56].

The clinical presentation of cisplatin-induced damage to the inner ear includes tinnitus and high-frequency sensorineural hearing loss. The hearing loss is usually modest but can be permanent and can progress to involve the lower frequencies. The tinnitus is often more irksome than the modest loss of hearing. The risk of inner ear damage is increased by prior irradiation and concomitant use of aminoglycosides.

Approaches to Protection

In general, patients who embark on antineoplastic chemotherapy are not only well monitored but also well informed. They are aware and have accepted the possibility of adverse consequences of drugs, including the development of tinnitus and some loss of hearing. Nevertheless, research on new methods of protection against ototoxicity (such as chemoprotection) is definitely needed. At present, the only strategy for reducing cisplatin-induced ototoxicity is based on limiting the total dose per cycle, the cumulative dose, and the dose intensity, which inevitably limits the antineoplastic effectiveness [57, 58]. Various strategies have been proposed to reduce cisplatin ototoxicity by chemoprotectants; in particular, an "upstream approach" to prevent the generation of ROS with antioxidants and a "downstream approach" using inhibitors of molecules involved in the apoptotic cell death pathway (such as caspases and p53). Indeed, the administration of several antioxidants does seem to be able to limit cisplatin ototoxicity [44, 59, 60]. Unfortunately, this approach has limited clinical usefulness because of the potential for negative interaction between antioxidants and antineoplastic drugs, resulting in reduced therapeutic effectiveness.

A particularly important issue in protection from cisplatin ototoxicity is the extensive use of this drug in pediatric patients, mainly because of its effectiveness in increasing the survival rate for children with cancer [47, 61, 62]. While new anti-cancer treatment protocols are very successful in improving pediatric patient survivals, they also subject the children to toxicities, which may profoundly affect a child's life and development [63, 64]. The reported incidence of cisplatin-induced ototoxicity in children varies from 10 to 85% of cases. Nevertheless, the implications of hearing loss to speech and language development are very important in very young children, whereas educational and psychosocial problems are more important for older children [63].

A child's age at treatment and the cumulative dose of cisplatin are the two most important risk factors in predicting moderate to severe hearing loss in children [62, 65]. During cisplatin therapy and a subsequent follow-up, pediatric patients should be audiometrically tested for the development of drug-induced sensorineural hearing loss [63, 66].

Several recent reports have shown a protective effect of amifostine, a thiolic cytoprotectant, in pediatric cancer patients treated with cisplatin [67–69]. However, evidence is contradictory, and more research is needed [70–72].

Chemotherapy of Parasitic Infections

Malaria is one of the most severe public health problems worldwide and a leading cause of death and disease in many third-world countries [73]. In Western world countries in which malaria has never existed or has been eliminated, the greater majority of cases occur either in travelers returning home or in migrants arriving from areas where malaria is endemic – "imported malaria" [74].

Each year, millions of people from malaria-free countries travel to areas where malaria is common and are therefore subjected to antimalarial chemoprophylactic treatment, which includes administration of several ototoxic drugs [75–78].

Quinolines and Related Compounds

Intravenous quinine dihydrochloride is currently the first-line antimalarial drug for the treatment of severe malaria in the UK [79]. Quinine is also sometimes

used for night cramps and chloroquinine for arthritis; chloroquine and hydroxychloroquine are also used in the treatment of rheumatoid arthritis and lupus associated arthritis. Quinoline derivatives are thought to exert their antimalarial effect by reaching high concentrations in the *Plasmodium* digestive vacuole and preventing the biocrystallization of toxic heme released during proteolysis of hemoglobin into hemozoin. Failure to inactivate toxic heme would poison the parasite, possibly via oxidative damage to plasma membranes [36, 80]. Quinolines are well absorbed from the gastrointestinal tract and may also be administered parenterally either by injection or by infusion. Although rare in western countries, quinine and quinidine overdose may lead to severe toxicity and death related to cardiovascular and neurological effects, particularly in children [81, 82]. Although several skeletal and muscular malformations have occurred in laboratory animals, quinoline derivatives appear safe in human pregnancy and during lactation [83–85].

Quinine is known to cause reversible hearing loss and tinnitus in both humans and animal studies [86–88]. Ototoxicity also has been reported in association with the use of other quinoline-type antimalarial drugs including chloroquine, hydroxychloroquine, and mefloquine [89–91]. The biological bases of quinolines-induced ototoxicity have not been fully resolved. However, some experimental evidence suggests that quinine may affect the function of calcium-dependent potassium channels and reversibly alter the mechanical properties of outer hair cells [92–95].

Approaches to Protection

Quinoline derivatives cause hearing impairment and tinnitus without vestibular disturbance. Both the hearing loss and the tinnitus are usually reversible, but the changes can progress to cochlear degeneration, permanent hearing impairment, and increased likelihood that the tinnitus will persist [96, 97]. Young and unborn children are probably more susceptible to quinoline-induced hearing loss [98, 99]. The ototoxic effects of quinine may be potentiated by doxycycline, an antibiotic, which is sometimes used with quinine in the prophylaxis or treatment of malaria [100]. On its own, doxycycline is not thought to be ototoxic. It has been reported that chloroquine-induced damage to the cochleovestibular system can recover if the medication is stopped and appropriate therapy is instituted with steroids and plasma expanders [89].

Mefloquine is also ototoxic, but in addition to hearing impairment and tinnitus, it may also cause vestibular disturbance [99, 101]. The tinnitus and hearing impairment are more likely to be permanent than with the other antimalarial drugs.

Salicylates

Acetylsalicylic acid (aspirin) was one of the first drugs to have come into common usage. Despite the introduction of new agents, it is still the analgesic, antipyretic, and anti-inflammatory drug most widely used in the world [102, 103]. Approximately 35,000 metric tones are produced and consumed annually, which is enough to make over 100 billion standard aspirin tablets every year [102, 104]. Besides its use as analgesic, antipyretic, and anti-inflammatory agent, aspirin is also extensively used in the prevention and treatment of various aspects of cardiovascular disease [105, 106], and it is under investigation in a number of other medical conditions including cancer [103, 107, 108].

Most pharmacological effects of salicylates are due to inhibition of prostaglandin formation via blockade of cyclooxygenase. Although there is no agreement about their molecular mechanisms of action, salicylates probably act because of their content in salicylic (orthohydroxybenzoic) acid [36, 102]. Aspirin also possesses distinct protein-acetylating capabilities, which may account for its unique pharmacological profile [109]. Salicylates are rapidly adsorbed from the gastrointestinal tract and well distributed in the body tissues and fluids. About 50% of orally administered aspirin is de-acetylated to salicylate in the liver immediately after absorption. Common metabolites are salicyluric acid, salicyl phenolic or acyl glucuronides, and gentisic acid. Salicylates are excreted in the urine. Plasma half-life of aspirin is about 15 min while the half-life of salicylate is between 2 and 12 h. Aspirin taken in low dose during pregnancy is generally considered safe. However, full-dose aspirin taken in the third trimester is considered to be in FDA pregnancy category D. Aspirin is excreted into human milk in small amounts and should be given to nursing mothers with caution [110].

Salicylates have been recognized as ototoxic longer than almost any other drug [111]. The main ototoxic

effects of salicylates are sensorineural hearing loss and tinnitus. Salicylate-induced hearing loss is typically mild to moderate, symmetrical, and flat or high frequency [112, 113]. The tinnitus is often described as a continuous high pitch sound of mild loudness. The neurobiological mechanism of salicylate-induced hearing loss and tinnitus remains obscure. However, several papers have shown that multiple actions of salicylates throughout the acoustic system may contribute. Salicylates administration profoundly affects cochlear function, possibly through downregulation of outer hair cells electromotile response with resultant decrease in cochlear neural output [114, 115]. Several other neurotransmitter systems are involved in salicylates ototoxicity at central level, including the glutamatergic and GABAergic system [112, 116–118]. Interestingly, sodium salicylate has been shown to partially protect against cisplatin ototoxicity and aspirin to partially protect against aminoglycoside ototoxicity, possibly because of their antioxidant properties [42, 119, 120].

Approaches to Protection

Salicylate-induced hearing loss is almost always reversible. Associated tinnitus usually subsides as hearing recovers, although this is not always the case. Quite large doses (6–8 g daily) are required to cause hearing loss and tinnitus [117]. The onset of tinnitus can be helpful as an early indicator of salicylate intoxication or salicylism [121, 122]. Salicylism is a potentially fatal poisoning that, partly because of the enormous amount of aspirin produced and consumed annually, remains a common cause for treatment in emergency departments, especially of children [123]. It is also noteworthy that salicylate intoxication is being reported increasingly often as a consequence of the use of herbal medicines [124–126].

Miscellaneous Drugs that are not Considered Ototoxic

Several different drugs may cause or aggravate tinnitus often without an effect on hearing. Some of these drugs may ease tinnitus in some patients, yet aggravate or cause it in others. Among these drugs are lidocaine, anticonvulsants, antidepressants, cannabinoids antihypertensives, β-adrenergic blocking agents, opioids (buprenorphine), caffeine, antihistamines, and several others. Unfortunately, the available evidence on the vast majority of these drugs is scarce and much of it anecdotal.

Lidocaine

Lidocaine is the prototypical amide-type local anesthetic, as well as one of the drugs most consistently reported as being efficacious in relieving subjective tinnitus. Available data consistently report that intravenous lidocaine is able to dose dependently inhibit tinnitus in approximately 60% of patients [127–130], although some authors report lower figures [131]. In some patients, tinnitus inhibition is complete, while in a small number of patients an exacerbation is perceived. Lidocaine is a voltage-gated sodium channel blocker able to reduce nerve cell responsiveness to stimuli in a time- and voltage-dependent fashion [132–134]. Lidocaine can also reversibly block voltage-gated potassium channels at concentrations compatible with plasma levels linked to tinnitus inhibition [135]. Since voltage-gated potassium channels are reported to play a key role in the encoding of auditory information, this effect of lidocaine may be relevant [136–139]. The site of action of lidocaine still remains unclear; earlier studies found a cochlear involvement [128, 140]; however, much evidence is now accumulating, which indicates a central site of action. In particular, auditory brainstem responses [141] and brain imaging techniques showed a central action of lidocaine and suggested that this drug may affect the functional linkage of several brain areas including auditory thalamus, auditory cortex, dorsolateral prefrontal cortex, and limbic system [142–144].

Anticonvulsants

Anticonvulsant drugs are increasingly used in the treatment of several nonepileptic conditions, including various psychiatric disorders, pain syndromes, and tinnitus [145]. Evidence of benefit from antiepileptic drugs in nonepileptic conditions varies among different drugs, but there is, in general, a lack of randomized double-blind trials in the literature [145, 146]. Diverse pharmacological mechanisms of action are responsible for the

therapeutic effects of antiepileptic drugs including effects on voltage-gated sodium and calcium channels, and neuronal inhibition mediated by γ-aminobutyric acid receptors. However, it may be hypothesized that the common final action is to reduce the tendency of neurons in sensory pathways to fire spontaneously or at inappropriately high frequencies. Carbamazepine, sodium valproate, and phenytoin are all incriminated as triggers and aggravators of tinnitus in some patients while they may help reduce it in others. Unfortunately, clear scientific evidence is unavailable at the moment.

Antidepressants

Antidepressants are widely used in many therapeutic protocols, including those for the management of tinnitus [147, 148]. This may be mainly because of the well-described comorbidity between major depressive disorders and tinnitus [147, 149, 150].

Among all antidepressants used for tinnitus, a particular interest has been paid to tricyclic drugs mainly because of the analgesic effect of this class of drugs [151, 152], in view of the proposed etiological correspondence between tinnitus and neuropathic pain [153, 154]. However, tricyclics may trigger or aggravate tinnitus in some patients. Amitriptyline has been reported as causing tinnitus in one case [155] and subsequently reported as being helpful in treating major depressive symptoms in tinnitus [156]. Recent evidence confirms the tinnitus-inducing effect of amitriptyline in some patients [157].

Selective Serotonin Reuptake Inhibitors (SSRIs) are the most widely prescribed antidepressants in many countries, mainly because of their clinical effectiveness and the reduced toxicity when compared to tricyclics. SSRIs are supposed to act by inhibiting the reuptake of serotonin into the presynaptic cell, thus causing a temporary increase in levels of 5-HT within the synaptic cleft. Despite their antidepressant effectiveness, SSRIs are frequently reported as inducing tinnitus either as a side effect of therapy or as a consequence of drug discontinuation syndrome [158–160]. Fluoxetine occasionally has a dramatic triggering effect, which may persist after the drug is stopped. The specific effectiveness of SSRIs in tinnitus has been recently questioned by several high-quality studies [148, 161, 162].

Among atypical antidepressants, the aminoketone bupropion acts as a norepinephrine and dopamine reuptake inhibitor and also as a nicotinic antagonist. Bupropion was originally marketed as an antidepressant but is now a fundamental drug in smoking cessation therapies along with nicotine replacement products [163, 164]. Bupropion is among the most frequently prescribed psychotropic drugs in the United States. It is not considered an ototoxic drug, but its association with tinnitus has been consistently reported in case reports as well as literature [165, 166]. Bupropion-induced tinnitus appears to be a temporary effect that disappears after the drug is discontinued. More research is needed to clarify the relationship between bupropion use and the development of tinnitus.

Cannabinoids

Cannabinoids (mainly tetrahydrocannabinol, cannabidiol, β-caryophyllene, and cannabigerol) are now being increasingly used in the treatment of several conditions including spasticity, multiple sclerosis, painful conditions (including neuropathic pain), asthma, and closed-angle glaucoma [167–169]. Natural and synthetic cannabinoids interact with the bodily endocannabinoid system by binding to specific G-protein–coupled cannabinoid receptors (CB1 and CB2). Agonists to CB receptors activate multiple intracellular signal transduction pathways, leading to a very complex picture involving inhibition of adenylate cyclase, activation of inwardly rectifying K channels, alteration of intracellular Ca levels, and influences on other ion channels and kinases [170–172]. Cannabinoid receptors are differentially expressed in the body tissues. CB1 is present in the brain and in the periphery it is present in adipose tissue, the gastrointestinal tract, skeletal muscles, heart, and in the reproductive system. CB2 is mainly expressed in the immune system [173].

As well as the chemically pure drug (such as Dronabinol and nabilone), cannabinoids are also available in some jurisdictions in the form of dried *Cannabis indica* leafs (marijuana). They are then generally self-administered by inhalation of marijuana smoke or through the gastrointestinal system. Despite consistent evidence of clinical efficacy and relative safety [174, 175], medical cannabis remains a controversial issue, mainly because marijuana is one of the most widely used recreational drugs in the world and remains illegal in many countries.

Cannabis smoke has been anecdotally reported to temporarily cause tinnitus in some patients, but

dramatically relieves it in some others. However, despite the reported occurrence of CB1 in the cochlear nucleus [176], there is no scientific evidence available of a direct role of cannabinoids in neurobiological basis of tinnitus [177]. However, more research on cannabinoids and tinnitus may be advisable, since a potential for clinical use may be obscured by other considerations. [175]

Drug-Induced Ototoxicity: Final Considerations

Ototoxicity is an adverse effect of several classes of drugs, such as the aminoglycosides, antineoplastic drugs, anti-inflammatory drugs, loop diuretics, antimalarial drugs, and others. Further, occasional cases of ototoxicity have been reported for a wide variety of other therapeutic compounds and chemicals.

Ototoxic agents can impair the sensory processing of sound at many cellular or subcellular sites. Much research has been performed to investigate the causes and the pathophysiology of ototoxicity to try to prevent this complication. However, the neurobiological mechanisms underlying ototoxicity have not been established for most of these drugs, and structure–toxicity relationships have not been determined. It is therefore quite difficult to predict the ototoxic potential of new drugs, and rational approaches to the prevention of ototoxicity are still lacking. In addition, the simultaneous administration of multiple agents, which are potentially ototoxic, can lead to synergistic loss of hearing. Exposure to loud noise may also potentiate hearing loss due to ototoxic drugs.

Drug-induced ototoxicity, although not life threatening, may induce considerable damage and cause severe disability. When increasing ototoxicity occurs, the ototoxic medication has to be discontinued if permanent hearing loss and/or tinnitus are to be minimized.

Although ototoxic injury is sometimes unavoidable, certain measures may reduce the risk. Prevention of drug-induced ototoxicity is generally based upon consideration and avoidance of relevant risk factors, as well as on monitoring renal function, serum drug concentrations, and cochlear and auditory functions before and during drug therapy.

Conclusions

- The treating physician should consider choosing a therapeutically equivalent nonototoxic drug whenever one is available, especially in patients with a heightened risk such as pre-existing cochlear hearing loss and renal insufficiency.
- During therapy with potentially ototoxic medications, the lowest dose compatible with therapeutic efficacy should be used.
- When indicated, periodically monitor serum peak and trough levels.
- Simultaneous use of multiple ototoxic medications (e.g., aminoglycosides and loop diuretics) should be avoided whenever clinical circumstances permit, as their concomitant use may increase the risk of permanent deficit.
- When early detection is important, audiological monitoring should include the very high frequencies as, generally, ototoxic drugs first destroy hearing in the very high frequencies, which are not normally tested (those above 8,000 Hz).
- Should a patient develop auditory (hearing loss and/or tinnitus) or vestibular (vertigo and/or disequilibrium) symptoms during therapy with a potentially ototoxic medication, audiometric testing and otological assessment should be arranged urgently especially if there is reluctance to stop the ototoxic medication.

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