Ototoxicity of Ototopical Drops—An Update

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Topical antibiotic solutions are frequently indicated in patients who have external or middle ear infections. It is well known that any substance that can enter the middle ear can access the inner ear via the permeability of the round window membrane (RWM) (and theoretically the annular ligament of the stapes/microfractures of the otic capsule), where it may cause adverse effects to the cochlear and vestibular apparatus [1]. The actual potential for ototoxicity of these ototopical preparations has been a subject of considerable debate. The introduction of non-ototoxic fluoroquinolone ear drops in 1997–1998, recent literature regarding the possible issues of unrecognized ototoxicity from ototopical preparations, and increasing litigation from alleged inappropriate use of ototopical drops has garnered significant attention among practitioners on the subject of ototoxicity from ototopical preparations. This ongoing debate led the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) to convene expert panels to review this issue and address the issue of ototoxicity of ototopical preparations and make an evidence-based recommendation regarding their use [2].

A recent survey in the United Kingdom noted that 98% of otolaryngologists would use drops in the presence of a tympanic membrane (TM) perforation, whereas only 43% of general practitioners would do the same for
fear of ototoxicity [3]. This article addresses the basic science, clinical re-
search, and clinical issues concerning the ototoxicity of ototopical prepara-
tions. Current AAO-HNS guidelines and position statements are reviewed.
The authors’ experience in giving expert testimony and consultation in med-
icolegal cases concerning ototoxicity of these drops is also summarized.

Causes of tympanic membrane perforation

The anatomic integrity of the TM may be disrupted by a surgical (therapeutic or diagnostic) procedure, trauma (blunt head trauma or blast injury), acute otitis media (AOM) or chronic infection (so-called “chronic suppurative otitis media” [CSOM]).

Tympanic membrane perforations associated with infection

Although relatively uncommon, AOM, if severe, may result in perforation of the TM with resulting acute otorrhea [4]. After perforation of the TM, the patient in some instances may develop a chronically draining ear (CSOM) with a persistent perforation of the TM [5]. Although the exact definition is debatable, chronic perforation associated with chronic mucosal disease (with or without cholesteatoma) with otorrhea of 3 months’ duration seems to be an acceptable definition of CSOM [6,7].

AOM frequently evolves into otitis media with effusion, however [5]. A persistent effusion often leads to myringotomy and insertion of pressure equalizing tubes (PETs) or tympanostomy tubes (TTs), which are placed in more than 1 million patients annually in the United States. Acute or chronic otorrhea from PETs may result from persistent middle ear or mastoid disease [5,8]. The reported frequency of post-tympanostomy tube otorrhea (PTTO) varies from 21% to 68%, depending on the study [9,10]. The 2000 Consensus Panel Report estimated the incidence of PTTO to be approximately 20% [5]; however, a recent meta-analysis suggested that the incidence could be much higher [11].

Microbiology

In patients with a perforated TM after AOM or patients who have an AOM complicating PETs, the most frequently cultured bacteria are Strepto-
coccus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis [12–14]. A recent study on PTTO recovered S pneumonieae in 17%, H influenzae in 18%, Staphylococcus aureus in 13%, and Pseudomonas aeruginosa in 12% and demonstrated that the causative organism is frequently not sensitive to oral antibiotics [15].

In patients who have CSOM, the most frequently cultured organisms are S aureus, P aeruginosa, and other aerobic and anaerobic organisms [16–18].
The microbiology of PTTO is often a combination of the organisms found in AOM and CSOM and varies with age and the number of infections. For example, *H influenzae, S pneumoniae, and Staphylococcus epidermidis* were cultured in children younger than 3 years (42%, 18%, and 16%, respectively), whereas *S aureus, P aeruginosa, and S epidermidis* were cultured in children older than age 3 years (39%, 24%, and 16%, respectively) [19,20].

Management of otorrhea

Topical antibiotics are recommended as first-line agents in uncomplicated cases [2,5]. Because ototopical antibiotics provide a high concentration of antibiotic directly into the middle ear, they should reduce the likelihood of the development of bacterial resistance. Ciprofloxacin hydrochloride and ciprofloxacin dexamethasone otic suspension and ofloxacin otic solution 0.3% contain concentrations 3000 \( \mu \text{g/mL} \) of ciprofloxacin and ofloxacin, respectively. Even if the causative organisms have previously developed partial resistance, the high concentration of antibiotic in the middle ear achieved with these topical drops undoubtedly exceeds the minimum inhibitory concentration of organisms encountered in the middle ear space. The risk for various systemic adverse effects, such as nausea, vomiting, diarrhea, and allergic reactions, also remains negligible with topical therapy.

Mechanisms of potential ototoxicity

Several years ago, a survey of otolaryngologists in the United States found that few were concerned about ototoxicity from topical medications in patients with TM perforations [21]. Whether ototopical solutions actually can pass through TM perforations or PETs and whether certain ototopical (especially aminoglycoside containing) antibiotics might cause a sensorineural hearing loss has been questioned by some clinicians [22].

The passage of otic solutions through PETs into the middle ear has been demonstrated using an artificial model of the ear [23]. In this model, massage of the tragus created pressures that exceeded those needed for passage of otic solutions through even small TTs [23]. In patients with active CSOM, instillation of a solution of gentamicin into the external auditory canal was associated with detectable plasma levels of gentamicin, which indicated systemic absorption [24]. Several reports in the literature described symptoms of ototoxicity after administration of ototopical agents in patients with TM perforations or TTs in place, which also indicated passage of the drops into the middle ear space [22–27]. Kaplan and colleagues [28] used commercially available gentamicin betamethasone otic drops as a solution for vestibular ablation in patients with Meniere’s disease. The drops were administered to patients with PETs in place and were consistently able to achieve a significant degree of vestibular ablation. This study clearly showed...
that commercially prepared otic drops not only can enter the middle ear space via a PET but also can cause significant ototoxicity.

The most likely route for medication to pass from the middle ear to the inner ear is through the RWM into the perilymph of the scala tympani [25]. The RWM is a three-layered structure that contains micropinocytotic vesicles in all three layers [29,30], which allows passage of many substances, such as electrolytes, peroxidase, and albumin [31]. The passage of substances into the inner ear is not just a passive phenomenon but involves three different mechanisms: diffusion, interepithelial transport, and intraepithelial transport. The permeability of the RWM was also found to increase approximately 48 hours after middle ear infection was experimentally induced [32,33]. Conversely, in patients with CSOM, the RWM may become thickened secondary to an immune response and the deposition of connective tissue (including mucosal web formation), which renders the membrane less permeable during this chronic inflammatory state [31]. One reason that any reduction in permeability of the RWM should protect the inner ear from the products of inflammation and conceivably, the potentially ototoxic components of ototopical preparations.

Ototoxicity of topical preparations

Ototoxicity (and nephrotoxicity) associated with systemic use of aminoglycosides was noted soon after the introduction of streptomycin by Waksman [34] in 1949. Newer agents (neomycin, 1949; gentamicin, 1963) were developed with the intent to introduce an effective and less toxic substitute [35,36]. These agents have demonstrated varying degrees of vestibular and cochlear toxicity, however. For example, in virtually all patients with prolonged high plasma levels of an aminoglycoside, vestibulocochlear damage occurs [37]. Even when the plasma levels of an aminoglycoside are within what has been considered to be a safe therapeutic range (ie, normal plasma peak and trough levels), some patients may develop ototoxicity (the aminoglycoside can continue to concentrate within the inner ear independent of its renal excretion/hepatic metabolism). In approximately 17% of patients who develop ototoxicity, a specific mutation (1555 A → G) of the mitochondrial 12S ribosomal RNA gene has been identified [37,38]. Whether there is a genetic susceptibility to ototoxicity from topically administered aminoglycosides is not known. Because of the risks associated with the use of systemic aminoglycosides, some clinicians have abandoned their use, particularly because equally effective systemic and topical alternatives without risk for ototoxicity are currently available [25,27,39].

In 1957, the potential for topical ototoxicity in humans was demonstrated by Schuknecht [40]. In his treatment paradigm, streptomycin was administered transtympanically for patients with incapacitating Meniere’s disease. Schuknecht achieved good results for the relief of vertigo, but this treatment usually resulted in a severe deafness in the treated ear.
The possibility that ototopical aminoglycoside preparations have the potential for ototoxicity has been investigated in several animal models. Several studies have documented the ototoxicity of various aminoglycosides when administered topically: gentamicin in bullfrogs [41], guinea pigs [42], and cats [43]; streptomycin in guinea pigs [44] and pigeons [45]; streptomycin and gentamicin in gerbils [46]; and neomycin in guinea pigs [47–49]. The deleterious effect of polymyxin B/neomycin/hydrocortisone on hair cells of chinchillas [50] and guinea pigs [51] also was documented. Some species differences were noted. In primates (ie, baboons), polymyxin B and neomycin caused hair cell loss and strial injury, although the hair cell loss was less severe than that seen in chinchillas [52].

Although the demonstrated ototoxicity of aminoglycosides in various laboratory animal models suggests that these drugs also are ototoxic in humans, interspecies differences in the anatomy and physiology of the RWM confound the predictability of the response. In humans, the structure of the RWM is similar to that of baboons (but thicker) and is much thicker than that of chinchillas [53]. The anatomic location of the round window niche in humans is such that it is not as exposed as in chinchillas and guinea pigs [31,54]. Overall, the extrapolation of results from animal studies to humans from topical ototoxicity should be done with caution [55].

Further evidence for the clinical ototoxicity of gentamicin is demonstrated by its intratympanic treatment of patients with Meniere’s disease [28,56–58]. In most cases the topical gentamicin solution used in intratympanic therapy for Meniere’s disease is prepared in the pharmacy using gentamicin solutions intended for intravenous administration. This preparation results in a high concentration of gentamicin being administered intratympanically (between 24 and 40 mg/mL, depending on whether the solution is buffered). One unique study, however, demonstrated that a commercially available ototopical gentamicin preparation (Garasone [gentamicin 3 mg/mL/1% betamethasone]) could ablate vestibular function if used in a prolonged fashion [24]. Most patients had objective evidence of a vestibulotoxic effect as judged by absent or diminished caloric responses on the treated side [28]. Unfortunately, 10 of 23 patients in this study had a worsening of their hearing, which indicated that this topical preparation containing gentamicin also could be cochleotoxic [28].

The ability of gentamicin to pass through the RWM into the inner ear was demonstrated in another unique study of patients who had Meniere’s disease or vestibular schwannomas who were scheduled for either labyrinthectomy or translabyrinthine surgery [59]. Gentamicin was injected into the middle ear either transtympanically before surgery (two patients) or intraoperatively through the facial recess. During surgery, samples of labyrinthine fluid, cerebrospinal fluid, and blood were obtained and analyzed for gentamicin [59]. The authors showed that gentamicin was concentrated in the labyrinthine fluid after transtympanic injection [59]. This study confirmed that as in animals, the RWM allows small molecules (ie, ≤1000 molecular weight) to
pass into the inner ear [59]. Each of the aminoglycosides—neomycin, streptomycin, gentamicin, kanamycin, and tobramycin—has a molecular weight <1000 molecular weight so that each may readily pass from the middle ear into the inner ear through the RWM [30,59].

Despite the widespread use of aminoglycoside drops worldwide, relatively few cases of ototoxicity seem to have been documented in the literature [60]. Cases that have been reported are primarily case reports or reports from relatively small series of patients [22,61–69]. Roland’s [70] review of the current world literature in 1994 estimated the incidence of ototoxicity (as measured by reports of hearing loss) from ototopical aminoglycoside drops to be approximately 1 in 10,000 or lower. The largest series of documented cases of ototoxicity with aminoglycoside drops were reported by Rutka and colleagues [1,28] in Toronto. They noted that ototoxicity may be underreported if hearing loss alone is used as a determination for documenting ototoxicity and that there was a greater incidence of vestibular symptoms in their series than hearing loss, especially from topical gentamicin preparations.

That Rutka and colleagues accumulated this series in Canada is not coincidental. The primary ototopical agent in Canada at the time was Garasone (gentamicin/betamethasone), whereas the aminoglycoside-containing ototopical agent with the largest market share in the United States was Cortisporin Otic (or the generic equivalent neomycin/polymyxin B/hydrocortisone). Overall, gentamicin has been found to be more vestibulotoxic than cochleotoxic, which may explain the greater incidence of acute vestibular loss and chronic disequilibrium from the Canadian studies. These adverse reports have led Health and Welfare Canada, the governmental department that oversees public health issues, to issue warnings as early as 1997 regarding the use of these drops in open or infected middle ears with a TM defect [71]. Informed consent warning patients of possible ototoxic side effects of aminoglycoside ear drops has been suggested [72] and was recommended by the 2004 AAO-HNS consensus panel in their evidence-based medicine and best practice review [2].

**Ototoxicity of other topical preparations**

*Nonaminoglycoside antibiotics*

Chloramphenicol, one of the first antibiotics to be used as an ototopical agent, has shown evidence of ototoxicity in animals [73,74]. Vasocidin ophthalmic solution has been used as an alternative to aminoglycoside-containing ototopical agents. Animal studies (chinchillas) have shown that this preparation has no toxic effect on inner ear function but is irritating to middle ear mucosa [75].

*Antifungal agents*

Fungal external otitis remains a commonly encountered and difficult-to-treat disorder. Currently, no topical otic agent exists that has been approved
by the US Food and Drug Administration for the treatment of otomycosis. Otolaryngologists, by necessity, have used multiple off-label topical antifungal agents in the treatment of otomycosis, with variable efficacy and safety. Merthiolate (thimerosal) has been reported to be effective for otomycosis [76] but has been banned for use as a topical antiseptic because it contains mercury [77].

In animal studies (guinea pigs), miconazole, clotrimazole, tolnaftate, and nystatin have demonstrated no evidence of ototoxicity when used as topical antimycotic agents [47]. Gentian violet, used for years as a topical antifungal agent, has shown significant evidence of ototoxicity in animal studies [47,78]. Cresylate and VoSol (hydrocortisone and acetic acid, nonaqueous 2%), commonly used as ototopical agents in the treatment of otomycosis, also have demonstrated evidence of ototoxicity in animal studies [79–81].

**Antiseptics**

In addition to Cresylate, VoSol, and gentian violet, other ototopical antiseptics have been implicated as having potential for ototoxicity. Ethanol has been studied in guinea pigs and povidone iodine has been studied in chinchillas, and both demonstrate evidence of ototoxicity [82]. Clinical evidence with betadine in ear surgery and with otorrhea management would suggest that it is safe, however.

Chlorhexidine, an antiseptic used for skin preparation for surgery, has been shown to cause ototoxicity if introduced to the middle ear [83]. Acetic acid and preparations that contain acetic acid, have been found to be toxic to isolated chinchilla cochlear outer hair cells [81]. Similarly, in chinchillas an otic solution that contained acetic acid was ototoxic, as demonstrated by changes in compound action potentials after the medications was instilled into the inner ear through the RWM [80].

**Corticosteroids**

Corticosteroids (hydrocortisone, dexamethasone) have been used in combination ear drops for years because of their anti-inflammatory effects. These agents, considered to be safe and effective, have been found to have a protective effect on the cochlea and are used transtympanically to reverse hearing loss and possibly control symptoms of Meniere’s disease [84]. Spandow and colleagues [85], however, showed in rats that topical application of hydrocortisone may lead to hearing impairment.

**Agents that provide a protective effect on the cochlea**

Although multiple agents have demonstrated cochlear and vestibular toxicity in animals and humans, many studies have focused on which drugs may have a protective effect on the inner ear. Agents that have shown a positive
protective effect (primarily against parentally administered drugs) include iron chelators [86,87], glutathione [88], corticosteroids [89], salicylates [90], alpha lipoic acid [48], glial cell line–derived neurotrophic factor [91,92], leupeptin [93], and N-methyl-D-aspartate receptor antagonists [94].

Efficacy and ototoxicity of fluoroquinolone-containing otic drops

Clinical studies that involve adults who have CSOM [95–98] and children who have PTTO [20,99,100] show no evidence of ototoxicity. Basic science and research studies have shown no evidence of ototoxicity with ciprofloxacin or ofloxacin [51,100–105]. Clinical studies support the efficacy of fluoroquinolones in the treatment of otorrhea associated with TTs [20,99,100,106–110] and in the treatment of CSOM [18,95–98,103,105,111–115]. The reader is referred to the cited references for further elaboration on these studies.

A chronology of evolving guidelines from the American Academy of Otolaryngology–Head and Neck Surgery concerning ototopical preparations

Historically the AAO-HNS adopted a position statement on ototopical antibiotics in 1994, which was reaffirmed in 1998, that recognized the appropriateness of treating ear disease with topical antibiotics, including aminoglycoside antibiotics.

In 2000, a consensus panel convened to address the issue of ototopical drops and their potential for causing ototoxicity. A summary of these recommendations is as follows [5]:

1. Topical antibiotics remain the first-line treatment of choice for uncomplicated otorrhea.
2. Non-ototoxic drops should be considered as first-line treatment of uncomplicated CSOM and PTTO.
3. The safety and efficacy of the non-ototoxic drops (ciprofloxacin, ofloxacin) have been established, but other issues, such as cost and availability, should be considered in selecting therapy.
4. Negligible risk exists when using ototoxic preparations when the TM is intact.
5. Culture-directed therapy is indicated when systemic antibiotics are required.

In 2004, a consensus panel convened by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) published the following guidelines in a March 2004 supplement to the Academy journal [2]:

1. When possible, topical antibiotic preparations free of potential ototoxicity should be preferred over ototopical agents that have the potential for ototoxic injury if the middle ear and mastoid are open.
2. If used, potentially ototoxic antibiotic preparations should be used only in infected ears. Use should be discontinued shortly after the infection has resolved.

3. If potentially ototoxic antibiotics are prescribed for use in the open middle ear or mastoid, the patient should be warned of the risk of ototoxicity.

4. If potentially ototoxic antibiotics are prescribed, the patient should be specifically instructed to call the physician or return to his or her office if the patient develops the following:
   a. Dizziness or vertigo
   b. Hearing loss
   c. Tinnitus

5. If the TM is known to be intact and the middle ear and mastoid are closed, then the use of potentially ototoxic preparations presents no risk of ototoxic injury.

Medicolegal issues

Recent attention has been given to medical cases in the United States and Canada involving litigation in which patients were claiming injury or negligence stemming from inappropriate use of ototopical preparations. Researching these medicolegal cases and their outcomes is difficult [60]. The exact number of these cases is unknown, but the same authors have given expert consultation and opinion in numerous cases in the United States and Canada. Some of the issues and recurrent themes from our combined experiences are outlined as follows:

- The symptoms of vertigo, not hearing loss, may predominate in these cases. A subjective complaint of vertigo, with or without objective findings (without objective evidence of hearing loss), may be the only complaint.
- Most cases occurred in patients treated after 1997–1998, the year in which fluoroquinolone drops were introduced. The AAO-HNS position statement on this issue was not published until June 2000, with a second, stronger, more definitive statement published in March 2004. These dates are significant because the March 2004 consensus statement is much stronger in recommending non-ototoxic alternatives. (See the AAO-HNS position statements in the previous section.)
- The fact that a safer and equally effective alternative ototopical agent (fluoroquinolone drops) without risk for ototoxicity was available and not used is emphasized.
- Treatment with drops for prolonged periods of time (> 7 days) or multiple refills of potentially ototoxic drops, especially when the otorrhea has ceased, without an intervening patient examination are significant.
- Ophthalmologic drops that contain potentially ototoxic antibiotics are particularly addressed because they are used off-label and are not
approved by the US Food and Drug Administration for use in the ear. Although frequently used and considered to be a superior alternative to many otologic drops, these drops have no written or approved indication for use in the ear, and this fact is often emphasized.

- Costs, availability, and insurance formularies are often not considered significant issues.
- Failure to provide the appropriate informed consent on the potential for the aminoglycoside containing drops to result in ototoxicity is emphasized, despite the fact that the need to give informed consent has been addressed only recently.

Summary

That ototopical drops can enter a PET or perforation and have adverse effects on the inner ear is no longer a topic of debate. The clinical incidence of ototoxicity, especially in the presence of inflammation, remains low but not insignificant, however. Recent literature suggests that this incidence, especially that of vestibular ototoxicity, may be underrecognized and underreported. Ototopical agents are a highly effective and powerful tool for clinicians and should be used as a first-line agent for otorrhea. Non-ototoxic preparations should be used when the clinical situation allows.

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References


