Safety of ofloxacin otic and other ototopical treatments in animal models and in humans

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To assess the safety of topical agents in the middle ear, animal studies were reviewed. Compared with aminoglycoside-containing preparations, which caused significant loss of hair cells in the basal turn of the cochlea, ofloxacin caused no loss of hair cells, even at concentrations higher than used clinically. Moreover auditory brainstem testing revealed no change in auditory thresholds in the ofloxacin-treated animals, whereas neomycin-treated animals showed substantial threshold shifts.

In human studies, use of topical ofloxacin 0.3% was not associated with any change in hearing. Topical ofloxacin has no demonstrable adverse effects on middle ear or cochlear function.

In the United States more than 750,000 children each year receive tympanostomy tubes for chronic otitis media. The objective benefits of this intervention in terms of improved hearing and decreased recurrent middle ear infections are well established, and a recent report documented an improved quality of life for treated children as well. However, the surgical procedure is not without risk, and resultant infection marked by otorrhea is relatively common. One-third of patients receiving tympanostomy tubes develop acute otitis media with otorrhea after surgery, and virtually 100% of those in whom the tube remains in place for more than 1 year will experience at least one episode of infection.

A wide range of antibiotics currently are used to treat otorrhea, but reversible and irreversible tinnitus and hearing loss have been reported as potential toxicities associated with acute intoxication or long term administration of many of these drugs. To best avoid these complications, a panel of experts convened by the American Academy of Otolaryngology-Head and Neck Surgery recently presented a set of consensus guidelines for antibiotic use in chronic suppurative otitis media, tympanostomy tube otorrhea and otitis externa. Their consensus is based on the failure of trial evidence to prove that systemic antibiotics improve outcome compared with ototopical preparations. The guidelines stress that topical antibiotics are first line treatment for these conditions and that, with consideration of the bactericidal activity and risk-benefit of the available pharmacologic choices, the most effective nontoxic option should be selected.

This article provides a review of the pathophysiology of drug-induced ototoxicity and the relative risk associated with different ototopical drugs. It will also attempt to describe the safety experience to date with the topical fluoroquinolone antibiotic, ofloxacin otic, which in early reports appears to cause little or no ototoxicity.

CONCERNS REGARDING OTOTOPICAL THERAPY

Today ototopical medications are the principal treatment for otorrhea caused by external otitis, chronic suppurative otitis media and acute otitis media associated with a perforation or tympanostomy tube. Treatment of otorrhea with topical agents is confounded by concerns about ototoxicity, which has been a substantial problem with aminoglycoside-containing preparations. Local and systemic uses of aminoglycosides have been reported to cause auditory and vestibular toxicity, including diminished hearing and vertigo. When administered to patients with otitis media with a tympanic membrane perforation, topical drugs may enter the middle ear and cause mucosal or tympanic membrane damage. Furthermore if the drug passes into the inner ear via the round window, it may cause cochlear and vestibular degeneration, ultimately leading to significant hearing loss and imbalance.

Potential mechanisms for drug-related ototoxicity have been evaluated in guinea pig models. In these animal systems, administration of antibiotic drops to the middle ear resulted in histologic damage to cochlear hair cells, with the most severe damage occurring at the basal turn of the cochlea. On auditory brainstem response testing the histologic changes noted with Cortisporin and gentamicin were associated with high frequency hearing loss. In humans the ototoxicity of gentamicin is administered intratympanically to disable the vestibular system in patients suffering from vertigo caused by Menière’s disease. In this...
setting gentamicin results in hearing loss in about 30% of cases. Other topical antibiotic agents, such as neomycin, consistently cause substantially greater prevalence and degree of loss and must be avoided in people with a perforated tympanic membrane and normal middle ear mucosa. In inflamed middle ears the risk of toxicity is reduced but not eliminated. Because of this risk continuing effort has been directed at identifying nonototoxic antibiotic medications.

**OFLOXACIN OTIC: ANIMAL EVIDENCE OF SAFETY**

The fluoroquinolone antibiotics have proved to be effective antimicrobials against the pathogens most frequently responsible for otorrhea, and in early reports they appear to be essentially nonototoxic. In particular ofloxacin otic has not been associated with cochlear or middle ear toxicity in animal models, while providing excellent activity against *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Pseudomonas aeruginosa*.

Barlow et al. at the University of Washington examined the effect of ofloxacin otic solution on the structure and function of the middle ear, ossicles and cochlea of albino Hartley guinea pigs. The investigators compared the toxicity of 1% ofloxacin otic solution, which is a dose three times the concentration contained in the preparation available for clinical use, Cortisporin otic solution, 0.3% gentamicin ophthalmic solution and benzalkonium chloride (0.026% and 0.05%) when administered to the middle ear of the guinea pigs for 7 days. Surface preparation light microscopy and scanning electron microscopy were used to evaluate toxicity to the hair cells of the organ of Corti, which amplify incoming signals for normal hearing. Figure 1 illustrates the results, revealing minimal (1%) cochlear inner and outer hair cell loss associated with ofloxacin otic exposure, compared with greater (6.5%) loss with gentamicin and significant hair loss (>65%) with Cortisporin. Benzalkonium, a vehicle used in the preparation of the solution forms of ofloxacin otic and gentamicin, also caused minimal toxicity.

The investigators also evaluated middle ear damage from the three antibiotics using scanning electron microscopy. When the animals were sacrificed, cross-sections of the middle ear mucosa indicated differential effects of the three drugs (Fig. 2). Gentamicin caused mild mucosal thickening and inflammatory cell infiltration, whereas Cortisporin produced severe mucosal thickening and inflammatory cell infiltrate. Ofloxacin otic 1%, on the other hand, caused minimal mucosal thickening that, in fact, was less than that associated with exposure to the benzalkonium medium. Although the mucosal effect of Cortisporin and gentamicin was not statistically significant compared with saline control, the finding indicates the potential for ototoxicity that must be considered when prescribing these drugs.

In a similar study Black et al. delivered 0.3 and 1.0% ofloxacin otic solution or 10% neomycin solution twice daily to the middle ear of guinea pigs (5/sex/group) for 30 days. After 1 month of treatment ofloxacin otic had not caused any damage to the middle ear mucosa or ossicles. There was no evidence of change in the auditory brainstem response (which is a functional measure of hearing) or to cochlear morphology. In addition there was no significant shift from baseline in mean threshold auditory responsivity when measured at 4, 10 and 20 kHz with either of the ofloxacin otic solutions. In contrast 10% neomycin caused a marked shift, in the range of 35.0 to 47.8 decibels (Table 1), indicating substantial hearing loss caused by drug-induced ototoxicity.

Overall animal studies of ototoxicity during topical ofloxacin otic administration have demonstrated a lack of local irritation, regardless of high concentrations of drug achieved locally. There has been no histologic or functional evidence of adverse effects on the mucosa or...
ossicles of the middle ear and inner ear. Based on these data, ofloxacin otic appears to be a safe topical antibiotic for application to the middle ear and is well tolerated even at concentrations three times that recommended for clinical use.

**CLINICAL SAFETY OF OFLOXACIN OTIC IN CHILDREN**

To confirm the lack of ototoxicity observed in animal models, the hearing of children enrolled in a large, multicenter, randomized parallel group study was examined. The study was designed to compare the safety and efficacy of 0.3% ofloxacin otic solution with that of amoxicillin oral suspension in the treatment of acute purulent otorrhea in children with tympanostomy tubes. The hearing tests were done on a subpopulation of children receiving 10 days of treatment with either 0.25 ml of 0.3% ofloxacin otic twice a day (n = 30) or 40 mg/kg/day amoxicillin suspension (n = 26) drawn from the total of 474 subjects enrolled in the safety and efficacy trial. These 56 children underwent audimetric testing to compare the safety of the two treatments on auditory function parameters: bone conduction threshold measures to determine the integrity and function of the inner ear; and air conduction threshold measures to evaluate middle and inner ear function. The children involved were >4 years old and had normal pretreatment sensorineural hearing.

Over the course of the study the subjects underwent standard audimetry and octave interval testing (500 to 4000 Hz) before therapy and at test of cure (Visit 4, Days 17 to 20) or failure visits. The target ear was the affected ear or the more severely affected ear in subjects with bilateral infection; if both ears were equally affected the right ear was designated as the target ear. The primary audiologic endpoint was a 10-dB change in air or bone conduction pure tone average (PTA) at 4000 Hz.

Results of the study are outlined in Table 2. There was no worsening of bone conduction parameters in either the target or nontarget ear associated with either ofloxacin otic or amoxicillin oral suspension therapy. In fact one patient in the ofloxacin otic group experienced a slight improvement in the nontarget ear. Air conduction measures revealed improvement or no change in 93% of ofloxacin otic-treated patients and 97% of the amoxicillin-treated subjects. However, more children in the ofloxacin-treated group (68%) showed improved hearing than in the amoxicillin group (35%), P = 0.029. These results indicate that ofloxacin otic and oral amoxicillin were equivalent in safety, with a trend toward benefit for ofloxacin in air conduction parameters, when administered to pediatric patients with acute otitis media caused by...
by tympanostomy tubes. Given the current American Academy of Otolaryngology-Head and Neck Surgery recommendation to use topical antibiotics for first line therapy, ofloxacin otic could be considered the agent of choice in purulent otorrhea through a tympanostomy tube.

CONCLUSION
Based on results of both animal and human studies, administration of ofloxacin 0.3% otic solution appears to be a safe and well-tolerated treatment for middle ear infections, including acute otitis media in children with a tympanostomy tubes. Ofloxacin otic therapy was not associated with changes to the ossicles in a guinea pig model, nor did it induce functional or histologic changes in the middle or inner ear as measured on both microscopic evaluation and audiologic brainstem response testing. In contrast hair cell damage and more inflammatory cell infiltration and muco-sal thickening were identified in animals treated with Cortisporin otic suspension and gentamicin ophthalmic solution. In the clinical trial setting ofloxacin otic did not adversely impact on hearing function in children treated for acute otitis media related to tympanostomy tube placement. For these reasons this agent can be considered a safe agent for use in first line therapy for patients with chronic suppurative otitis media and acute otorrhea in children with tympanostomy tubes.

REFERENCES
1. CDC Survey of Ambulatory Surgery.