Oxymetazoline, Mupirocin, Clotrimazole—Safe, Effective, Off-Label Agents for Tympanostomy Tube Care

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Abstract

Objectives: Only a few medications have a United States Food and Drug Administration indications for prevention and/or treatment of infections in patients with tympanic perforations or tympanostomy tubes. We examined 3 off-label agents that have become important in tympanostomy tube care hoping to demonstrate the effectiveness and safety of each in experimental assays and human application. Methods: Computerized literature review. Results: (1) Oxymetazoline nasal spray applied at the time of surgery is equivalent to fluoroquinolone ear drops in the prevention of early postsurgical otorrhea and tympanostomy tube occlusion at the first postoperative visit. (2) Topical mupirocin 2% ointment is effective alone or in combination with culture-directed systemic therapy for the treatment of tympanostomy tube otorrhea caused by community-acquired, methicillin-resistant Staphylococcus aureus. (3) Topical clotrimazole 1% cream is highly active against the common yeast and fungi that cause otomycosis. A single application after microscopic debridement will cure fungal tympanostomy tube otorrhea in most cases. None of these 3 agents is ototoxic in animal histological or physiological studies, and each has proved safe in long-term clinical use. Conclusions: Oxymetazoline nasal spray, mupirocin ointment, and clotrimazole cream are safe and effective as off-label medications for tympanostomy tube care in children.

Keywords
clotrimazole, mupirocin, off-label medications, otorrhea, oxymetazoline, tympanostomy tubes

Introduction

Only a few medications have a United States Food and Drug Administration (FDA) indications for treatment or prevention of infection in patients with tympanic perforations and/or tympanostomy tubes. Most are fluoroquinolone antibiotic preparations. These drugs form a foundation for the management of post-tympanostomy tube otorrhea (TTO) and are very effective.¹ At the same time, they are expensive, unnecessarily broad in antimicrobial spectrum and ineffective against certain resistant bacteria and fungi.

Off-label prescribing refers to the use of medicines outside of the indications for which they are licensed by national regulatory bodies. Off-label prescribing is quite common in children, as most drugs are developed only on the basis of trials with adults.² Further, new indications for established, inexpensive drugs are seldom sought by for-profit pharmaceutical companies. Although American physicians are permitted to use FDA-approved medications for alternative indications and in nonapproved populations, this should be done only when there is good evidence of efficacy and safety.

This article will examine 3 off-label agents that have become important in tympanostomy tube care. We will present evidence for the effectiveness of each in its specific clinical setting and demonstrate the safety of each in experimental assays and human application.

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Oxymetazoline Solutions for the Prevention of Postoperative TTO and Tube Occlusion

Perioperative otorrhea remains a relatively common complication of tympanostomy tube placement surgery. Approximately 10% to 20% of children who undergo placement of tympanostomy tubes develop early-onset otorrhea due to bacterial infection. There is a lack of consensus among otolaryngologists regarding whether prophylaxis against early-onset tube otorrhea is routinely warranted, which ear drops are most effective and least harmful, and what dosing regimen should be used. Only a few products are FDA approved for treatment of TTO and just one product is FDA indicated for the prevention of postsurgical TTO. All of these are broad-spectrum fluoroquinolone drops—without or without an added steroid. In a single randomized placebo-controlled trial, the administration of topical ciprofloxacin at the time of surgery reduced the rate of otorrhea at 2 weeks after surgery (11% vs 29%). A subsequent randomized trial did not find a statistically significant reduction in the rate of early otorrhea in patients treated postoperatively with topical ciprofloxacin compared with normal saline (17% vs 24%, respectively).

Broad-spectrum antibiotic drops have been associated with the development of fungal otitis and emergence of resistant microbial pathogens. All of the FDA-approved ototopical drops are expensive and some are not commonly covered by major insurance carriers. Given these concerns, our group began using generic oxymetazoline nasal spray as an alternative to antibiotic ototopicals after tube surgery 20 years ago. Oxymetazoline nasal spray is available in most operating rooms, has excellent hemostatic properties, and seems to work as well as quinolone drops for preventing early post-TTO and tube occlusion.

To prove that oxymetazoline was both safe for use in children and effective in preventing the common post-tube complications, our group undertook 2 studies in the early 2000s. In the first study, oxymetazoline was compared to ciprofloxacin in young children undergoing tympanostomy tube placement for common indications. Data from 488 children were recorded. Patient ages ranged from 6 months to 14 years. Ciprofloxacin solution was used with 219 patients. Two hundred sixty-nine patients received oxymetazoline drops. One hundred eighty-seven (38%) patients had bilateral dry middle ear clefts at the time of surgery. Mucoid effusions were found in 41% of patients. Serous and purulent effusions were recorded in 16% and 4% of patients. The incidences of postoperative otorrhea for patients who received oxymetazoline drops and ciprofloxacin drops were 10% and 7%, respectively. There was no difference found between ciprofloxacin and oxymetazoline solutions and the occurrence of postoperative otorrhea (odd ratio = 1.4, 95% confidence interval = 0.718-2.725; P = .32). The overall incidence for postoperative otorrhea was 8.9%.

In a second experimental study, 9 strains of Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa, Moraxella catarrhalis, Streptococcus pneumoniae penicillin resistant, S pneumoniae penicillin intermediate, and S pneumoniae penicillin sensitive were studied in a disc diffusion model. Discs were impregnated with clinical dosages of United States Pharmacopeia (USP) oxymetazoline, 2 oxymetazoline commercial preparations Visine LR (Pfizer, Morris Plains, New Jersey) and Nasal Relief Spray (Clay-Park Labs, Inc, Bronx, New York), ciprofloxacin, (Ciloxan; Alcon Laboratories, Inc, Fort Worth, Texas), or ofloxacin (Floxin; Daiichi Pharmaceutical Corp, Montvale, New Jersey).

United States Pharmacopeia oxymetazoline had little activity against the common pathogens of otitis media. Commercial preparations of oxymetazoline (which contained antimicrobial preservatives) caused modest inhibition of growth for Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, and S pneumoniae (penicillin sensitive, intermediate resistant, resistant). Pseudomonas aeruginosa was not inhibited by any of the oxymetazoline preparations. As expected, ciprofloxacin and ofloxacin drops produced zones of inhibition at least twice the size of those from the oxymetazoline preparations.

In the ototoxicity portion of the study, guinea pig middle ears were exposed to the 5 experimental agents and well, as gentamycin and saline controls. The excised cochleas were fixed and examined by scanning electron microscopy for loss of outer hair cells in the basal cochlear turn 2 weeks after chemical exposure. In the saline-exposed group and Visine L.R. exposed guinea pigs, a mean of 1.04 ± 1.04% of their outer auditory hair cells were missing. This is contrasted by the gentamicin-exposed animals, in which a mean loss of 8.33 ± 2.95% of outer auditory hair cells occurred in response to this known ototoxic agent. No loss of outer hair cells (0.00%) was observed in the guinea pigs that received treatment with either Nasal Relief Spray or USP oxymetazoline.

Critics have worried about oxymetazoline’s potential effects on cochlear blood flow and hearing. In response, Sam Daniel’s team in Montreal studied distortion product otoacoustic emissions before and 1 day after middle ear exposure to oxymetazoline solutions in chinchillas. They confirmed that oxymetazoline was not ototoxic and caused no acute change in otoacoustic emissions in this animal model.

We have used oxymetazoline nasal spray during tube placement for the last 20 years. There has been no suggestion of ototoxicity on postoperative audiograms throughout this experience with 10 000 tube placements. Our prevalence of TTO otorrhea remains similar to that in published series.

Commercially available oxymetazoline preparations are not ideal. Oxymetazoline nasal spray is acidic and stings, especially after tube placement in dry (no effusion) ears. In response to parental feedback, we have changed our postoperative protocol in the last decade. We still use oxymetazoline at the time of tube placement, but substitute pH neutral, ciprofloxacin generic eye drops following surgery (5 drops of ciprofloxacin solution, twice daily, for 3 days).

Mupirocin 2% Ointment to Treat Community-Acquired Methicillin-Resistant Staphylococcus aureus TTO

Otorrhea is the most common adverse sequela of tympanostomy tube insertion. In children less than 3 years of age, TTO
is caused by the common pathogens of acute otitis media—*S. pneumoniae, Haemophilus influenzae, and Moraxella catarrhais*. In older children and those who have been treated with antibiotics, *Staphylococcus aureus* and *Pseudomonas aeruginosa* grow more commonly in cultured otorrhea discharge.13

There is no standard treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) otitis externa. Currently, only fluoroquinolone drops are FDA approved for topical treatment of acute TTO. Although some have argued that the high concentration of fluoroquinolones in ototopical preparations should overcome resistant strains,14 fluoroquinolone drops fail in more than 50% of MRSA-TTO.15

In our practice, children presenting with uncomplicated otorrhea are treated empirically with fluoroquinolone drops. If ototopical drops fail, or cannot be effectively instilled due to copious otorrhea, an oral antibiotic with activity against the common pathogens of acute otitis media is prescribed. Children with severe illness or those who fail ototopical drops and/or appropriate empiric systemic therapy are seen in the office, their ears are suctioned under the operating microscope and the discharge is sampled at the tube orifice. This material is routinely sent for Gram stain and aerobic culture. Following this otorrhea protocol, between 10% and 20% of cultures of refractory infections grow MRSA. This occurs more often in families working in health-care occupations and much more often in children who have previously had cultures positive for MRSA.16

Encouraged by early reports of efficacy in treatment of adult chronic otorrhea17 and animal studies demonstrating lack of ototoxicity,18 we began routine use of topical mupirocin as an adjunct to culture-directed systemic therapy in 2014. Over the last 6 years, we have treated MRSA-positive infections with topical mupirocin (single application of 1 mL of 2% mupirocin ointment to the tympanostomy tube, tympanic membrane, and external auditory canal with a 3-mL syringe and 18-gauge intravenous catheter under microscopic guidance). Initial, we used topical mupirocin in combination with systemic therapy (oral trimethoprim-sulfa, clindamycin, or linezolid).19 In the first 12 patients treated this way 12/12 were cured, compared to 15/24 treated with systemic therapy alone.20

Based on this favorable result, we have used topical mupirocin monotherapy (no systemic treatment) for the last 3 years with a similar high initial cure rate. There have been no new sensorineural hearing losses in the mupirocin-treated children. There is a significant rate of MRSA recurrence in subsequent otorrhea episodes (approximate 50%), but topical mupirocin has remained effective during repeat treatment.

Infectious disease guidelines recommend topical decolonization for children who have had multiple MRSA recurrences.21 This includes mupirocin ointment to the nares 2 to 3 times per day for 1 week each month for 3 months, dilute bleach baths twice per week for 3 months, chlorhexidine baths or showers once daily on the days of the week that bleach baths are not given for 3 months. Whether decolonization of the skin and anterior nares will decrease nasopharyngeal colonization or the incidence of recurrent MRSA TTO is not known.

Topical 2% mupirocin ointment delivers a high dose of an effective agent for several days duration. In combination with mechanical debridement, it controlled infection by MRSA without evidence of local reaction or subsequent hearing loss in a single small series.

**Topical 1% Clotrimazole Cream for the Treatment of Fungal Otitis Externa and Fungal TTO**

Broad-spectrum antimicrobials are frequently used for the treatment of acute otitis externa as well as acute TTO. These agents typically contain a combination of antibiotics covering both Gram-positive and Gram-negative organism, often with the addition of a moderate to high strength steroid. These agents are very effective in both clinical settings. When symptoms do not resolve as expected, it is common for primary care providers to extend or repeat the same therapy—often with the additional of an oral antibiotic. This cycle of treat, fail, repeat can overwhelm normal skin flora and lead to fungal overgrowth.22

Fungal otitis externa typically presents with aural discharge, itching or pain, excoriation of the meatal skin, and conductive hearing loss. The species causing fungal infection in the ear include molds, yeasts, and occasionally, dermatophytes. *Aspergillus* and Candida species are commonly isolated while *Mucor, Fusarium, Scedosporium, Hendersonula, Rhodotorula, and Cryptococcus* are rare.23 Candida species are commonly associated with thick, white semisolid ear canal discharge. In contrast, black hyphae are visible during otomicroscopy in *Aspergillus* infections.

Mechanical debridement, drying of the ear canal, discontinuation of broad-spectrum antibiotics, and application of antifungal agents are standard in the treatment of fungal otitis externa.24 Topical antifungals, such as clotrimazole, miconazole, bifonazole, ciclopirox olamine, and tolnaftate, have all been advocated for the treatment of otomycosis in patients with an intact tympanic membrane. Systemic antifungal agents are effect for the treatment of cutaneous fungal infections and have been used to treat rare cases of invasive fungal otomycosis.25

Since the use of fluoroquinolones became widespread, an increase in the incidence of fungal TTO has been observed.26 Anecdotally, recent exposure to ofloxacin and amoxicillin–clavulanate is very common in children presenting with fungal TTO.27 No agent is FDA approved for the treatment of fungal TTO. Thus, clinicians have used topical antifungals in an off-label fashion for several decades.

In 1988, Stern et al28 used a disc diffusion assay to measure the effectiveness of 13 antifungal agents against 15 fungi and yeasts collected from their otomycosis patients. Among these agents, 1% clotrimazole solution had the largest zones of inhibition with nystatin, amphotericin B, miconazole, and nata-nymycin also showing lesser activity. More recently, Dundar and Iynen29 treated otomycosis patients with mechanical debridement and a single instillation of 1% clotrimazole cream. This

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*S. pneumoniae, Haemophilus influenzae, and Moraxella catarrhais* grow more commonly in cultured otorrhea discharge.13
eradicated fungal otomycosis in 39 of 40 adult patients—some of whom had tympanic perforations. Jimenez-Garcia et al treated 50 adult patients with debridement and either a single instillation of clotrimazole cream or with daily self-application of tolnaftate solution for 7 days. Of this, 75% of clotrimazole patients were free of infection at 1 week (vs 47% of tolnaftate-treated patients).

In his Triological thesis, Lawrence Tom examined the safety of common antimycotic agents in a guinea pig model. He found that clotrimazole, miconazole, nystatin, and tolnaftate did not cause cochlear hair cell loss after weeklong middle ear exposure to these agents. The neomycin control cause severe hair cell loss and gentian violet exposure caused pronounced behavioral signs of vestibular damage, as well as extensive middle ear inflammation and new bone growth on histological examination.

Our group has treated fungal otitis externa and fungal TTO with mechanical debridement and topical clotrimazole for 20 years. We initially used 1% clotrimazole solution applied once following office debridement, then administered by caregivers at home daily for a week. We stopped using clotrimazole solution in children with nonintact ear drums after parents complained that their children experienced pain lasting for hours. Instead, we substituted 1 to 1.5 mL of 1% clotrimazole cream instilled under the operating microscope after mechanical debridement with suction. Since 2002, 157 children have been treated in this manner. One hundred forty-six were cured at follow-up. Seven children required between 2 and 5 topical treatments to achieve control. Four children recurred more than a month later and were retreated in the same manner. No child has presented with new-onset hearing loss or vestibular symptoms follow treatment with topical clotrimazole cream.

Off-label use of topical 1% clotrimazole cream following mechanical debridement is safe and effective for control of outer ear infections caused by yeast, fungi, and molds. There is no evidence of ototoxicity in experimental models or in clinical practice in children with tympanostomy tubes. Some children require repeat treatment for control of signs and symptoms of fungal infection.

Conclusion
There are only a few medications approved for the prevention and treatment of TTO. Unfortunately, the lengthy and expensive government certification process has limited the number and type of agents carrying FDA indications to fluoroquinolone antibiotics with or without a steroid components. Although effective in the most common settings, this limited pharmacopeia is insufficient for managing certain refractory infections. This article has examined the off-label use of 3 FDA-approved preparations and attempted to demonstrate their safety and efficacy using animal experiments and clinical experience.

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