Ciprofloxacin 0.3%/Dexamethasone 0.1% Sterile Otic Suspension for the Topical Treatment of Ear Infections

A Review of the Literature

G. Michael Wall, PhD, David W. Stroman, PhD,* Peter S. Roland, MD,† and Joseph Dohar, MD‡*

Abstract: The objective of this article is to review the literature related to ciprofloxacin 0.3% and dexamethasone 0.1% sterile otic suspension. A systematic literature search utilizing Medline was conducted to identify peer-reviewed articles related to safety and efficacy. A total of 47 publications were identified and reviewed herein. The literature supports the use of antibiotic/antiiflammatory combination ear drops in the treatment of both acute otitis externa and acute otitis media in pediatric patients with tympanostomy tubes. Ciprofloxacin/dexamethasone has been demonstrated as safe and effective with regard to clinical cures and microbiological eradication of pathogens in either disease with low treatment failure rates. Additionally, the literature also provides clear evidence for the contribution of dexamethasone when added to ciprofloxacin for the topical treatment of ear infections.

Key Words: ciprofloxacin, dexamethasone, acute otitis externa, acute otitis media

(*Pediatr Infect Dis J* 2009;28: 141–144)

The treatment of ear infections has been discussed in the literature since 1500 BC[1]and ear drops used since antiquity have included astringents, antiseptics, alcohol, benzoin, and various powders. Antibiotics, however, have become the most effective means of therapy since the middle of the 20th century.[1] From the late 1950s to late 1990s in the United States, the ear drops of choice have been combinations of neomycin, polymyxin B, and hydrocortisone. Aminoglycosides, lipopeptide antibiotics, and other ingredients of older ear drop formulations have been shown to cause ototoxicity.[2–4]

In the last decade, 3 fluoroquinolone ototopical antibiotic formulations have been proven safe and effective for the topical treatment of ear infections and approved in accordance with current rigorous regulatory requirements including ototoxicity evaluations: (1) ciprofloxacin 0.3%/dexamethasone 0.1% (Ciprodex Sterile Otic Suspension),[5] (2) ciprofloxacin HCl 0.2%/hydrocortisone 1% (Cipro HC Otic Suspension)[6] (Ciprodex and Cipro are registered trademarks of Bayer AG, licensed to Alcon Laboratories, Inc., Fort Worth, TX), and (3) ofloxacin 0.3% (first approved as Floxin Sterile Otic Solution[7]; Floxin is a registered trademark of its owner; now generic). Although all of the quinolone-containing ear drops are approved for the treatment of acute otitis externa (AOE), only ciprofloxacin/dexamethasone and ofloxacin are sterile and approved by the US Food and Drug Administration (FDA) for the topical treatment of acute otitis media in patients with tympanostomy tubes (AOMT). Of these, ciprofloxacin/dexamethasone is the only antibiotic/anti-inflammatory fixed combination ear drop product approved for the topical treatment of AOMT. The purpose of this article is to review the scientific literature pertaining to ciprofloxacin/dexamethasone.

Accepted for publication August 14, 2008.
From the *Alcon Research Ltd, Fort Worth, TX; †Department of Otolaryngology, University of Texas Southwestern Medical School, Dallas, TX; and ‡Department of Otolaryngology, Children's Hospital of Pittsburgh, Pittsburgh, PA.
Drs. Wall and Stroman are Alcon employees and stockholders. Drs. Roland and Dohar are consultants for Alcon.
Address for correspondence: Julie Crider, PhD, Alcon Laboratories, Inc. (TA6-2), 6201 South Freeway, Fort Worth, TX 76134-2099. E-mail: Julie.Crider@AlconLabs.com.

ISSN: 0891-3668/09/2802-0141
DOI: 10.1097/INF.0b013e31818b0c9c

METHODS

A systematic literature search was conducted to identify peer-reviewed articles related to ciprofloxacin/dexamethasone utilizing Medline with the search terms "ciprofloxacin"or "ciprodex" and any of the following terms separately or in a combination thereof: "ototopical," "antibiotics," "drops," "treatment," "resistance," "otitis externa," "otitis media," "tympanostomy tube," "otorrhea," "draining ear," "side effects," and "complications." A manual search was also conducted, based on citations in the published literature and reports were referenced at the authors' discretion if deemed applicable to the subject matter of the review.

Treatment of Ear Infections With Ear Drops

Today, ear drops are prescribed mainly for the topical treatment of ear infections and associated inflammation. Although ear infection can occur at any age, it is one of the most common childhood diseases.[8] Ear infections are broadly divided into those affecting the outer ear canal and the middle ear space.

The most common ear infection is AOE or "Swimmer's Ear." The major recognized AOE pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[9] A June 2000 consensus panel report from the American Academy of Otolaryngology-Head and Neck Surgery Foundation recommended the use of topical preparations for the initial therapy for the most common type of uncomplicated AOE, diffuse otitis externa (OE).[10] In general, systemic antimicrobial therapy is recommended if there is extension outside the ear canal or in the presence of specific host factors such as a compromised immune system.[11]

Middle ear infections frequently begin as a result of upper respiratory pathogens entering the middle ear space via the Eustachian tube, often resulting in inflammation manifested as effusion. If otitis media recurs despite repeated regimens of oral antibiotics, it is often treated by the surgical insertion of tympanostomy tubes (TT) to ventilate the middle ear space. This is the most common surgical procedure for children in the United States, with approximately 2 million surgeries annually.[12] Post-TT otorrhea is the most frequent complication after insertion of ear tubes: an evidenced-based review reported an incidence rate in the range of 15% to 19% with wide variation from 3.4% to 74%.[13] The major recognized bacterial pathogens from AOMT are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *S. aureus*, and *P. aeruginosa*.[14] The consensus panel report[10] also concluded that in the absence of systemic infection or serious underlying disease, topical antibiotics alone should constitute first-line treatment for most patients with tympanostomy tube otorrhea, finding no evidence that systemic antibiotics alone or in combination with topical prepara-

tions improve treatment outcomes compared with topical antibiotics alone.

Pharmacokinetics

The pharmacokinetics of ciprofloxacin/dexamethasone was studied in 25 pediatric patients (age, 1–14 years) by instilling a single dose (0.42 mg ciprofloxacin and 0.14 mg dexamethasone) in each middle ear through the TT immediately after tube placement.[15] The mean maximum concentration (C_{max}) of ciprofloxacin in plasma of children was 1.33 ± 0.96 ng/mL and the mean plasma half-life ($t_{1/2}$) was 3 ± 1.2 hours. The mean $C_{max}$of dexamethasone was 0.90 ± 1.04 ng/mL (range, <0.05–5.10 ng/mL) and the mean $t_{1/2}$ was 3.9 ± 2.9 hours.

Microbiology of AOE

Roland and Stroman reported on external ear canal specimens collected from 1998 to 2000 from 2039 subjects clinically diagnosed with AOE.[9] The studies revealed that summer is the peak season for AOE—80% of cases occurred in the summer months versus 20% of the cases during the rest of the year. The most frequently recovered bacteria were *P. aeruginosa* (38%), *S. epidermidis* (8.9%), and *S. aureus* (7.7%).

Microbiology of AOMT

Roland et al[14] summarized the findings of 4 separate clinical studies (2000–2001) on the recovery of 1309 organisms from the 956 pretherapy specimens of children with draining ear tubes. There were age and seasonal variations in the microbiology of AOMT. For example, in age group 0–2 years, 45% of the children had *H. influenzae* and/or *S. pneumoniae*. In the age group 3–5 years, only 15% of children had *H. influenzae* and/or *S. pneumoniae*. Bacterial recovery from draining ears was greatest in summer (95%) and lower in winter months (75%). The most frequently recovered organisms from these AOMT patients were: *S. pneumoniae* (17%), *H. influenzae* (14%), *S. aureus* (13%), *P. aeruginosa* (12%), *Staphylococcus epidermidis* (10%), and *M. catarrhalis* (4%).

Ototoxicity

No ototoxicity has been reported to date for ciprofloxacin.[5,6,16–19] In a study of patients undergoing removal of acoustic neuroma, 0.5 mL ciprofloxacin solution was instilled into the middle ear. No ciprofloxacin was detected in the labyrinthine fluid, (suggesting a lack of absorption through the round window membrane), cerebrospinal fluid, or serum samples.[19]

Literature reports of ototoxicity for topical corticosteroids have been inconclusive. Some authors have reported ototoxicity to ear drops containing hydrocortisone and aminoglycosides,[20–23] though these reports focused on the aminoglycoside components, which are known to be ototoxic.[2] Spandow reported that intratympanic application of a 2% hydrocortisone formulation resulted in altered auditory brainstem responses in rats but no cochlear damage by light or electron microscopy.[24] Kaplan et al reported decreased distortion-product otoacoustic emissions in chincillas intratympanically treated with 0.2% ciprofloxacin/1% hydrocortisone but no evidence of hair cell damage.[25] Studies of 0.1% dexamethasone phosphate in cat ears[26] and hydrocortisone 17-butyrate 21-propionate in rat ears[27] revealed no ototoxicity. Likewise, combinations of ciprofloxacin with either 0.1% dexamethasone[5] or 1% hydrocortisone[6] were nontoxic to the guinea pig cochlea when administered twice daily for 28 days in FDA-approved studies. Some studies have even demonstrated an otoprotective effect of corticosteroids.[28,29] Irrigation of the guinea pig bulla with ciprofloxacin/dexamethasone after semicircular canal transection did not damage hearing[30] and administration of ciprofloxacin/dexamethasone to myringotomized rats, with or without Eustachian tube obstruction, led to significantly slower wound healing at day 7 (but not at day 28) than in the untreated and balanced salt solution-treated animals.[31]

Clinical Trials for AOE

Two prospective, randomized, observer-masked, active-controlled, multicenter clinical trials were conducted for ciprofloxacin/dexamethasone in the treatment of patients with AOE[32–35] (Table 1). Both trials randomized patients 1 year and older with intact TM and symptoms of AOE at sites across the United States. Signs and symptoms of AOE were assessed on days 3, 8 (end of therapy), and 18 (test of cure). Microbiologic eradication (presumed or documented) and frequency of adverse events were also assessed.

TABLE 1. Comparative Clinical Studies Evaluating the Efficacy of Ciprofloxacin/Dexamethasone in Adults and Children With Ear Infections

Infection Type	Reference	Study Design (Duration)	No. Patients Enrolled	Treatment Regimen	Outcome, % (No. Cures/No. Evaluable)	
					Microbiological	Clinical pp
Otitis externa, 1 yr and older	32	r, p, om, ac, mc (14 d)	909	Ciprodex: 3dr (ped)/4dr (adult) bid × 7 d Ciloxan: 3dr (ped)/4dr (adult) bid × 7 d vs. Cortisporin: 3dr (ped)/4dr (adult) tid × 7 d	Ciprodex: 87% (198/229) Ciloxan: 87% (206/236) Cortisporin: 85% (184/217)	Ciprodex: 87% (227/262) Ciloxan: 86% (235/274) Cortisporin: 84% (208/249)
Otitis externa, 1 yr and older	32	r, p, om, ac, mc (14 d)	468	Ciprodex: 3dr (ped)/4dr (adult) bid × 7 d vs. Cortisporin: 3dr (ped)/4dr (adult) tid × 7 d	Ciprodex: 92% (158/172) Cortisporin: 85% (146/171)	Ciprodex: 94% (189/202) Cortisporin: 89% (185/208)
AOMT (ped), 6 mos to 12 yrs	32	r, p, om, ac, mc (14 d)	201	Ciprodex: 3dr bid × 7 d versus Ciloxan: 3dr bid × 7 d	Ciprodex: 90% (66/73) Ciloxan: 80% (51/64)	Ciprodex: 91% (76/84) Ciloxan: 80% (58/73)
AOMT (ped), 6 mos to 12 yrs	32	r, p, om, ac, mc (18 d)	599	Ciprodex: 4dr bid × 7 d versus Floxin: 5dr bid × 10 d	Ciprodex: 91% (165/181) Floxin: 82% (139/170)	Ciprodex: 86% (202/236) Floxin: 79% (174/220)
AOMT (ped), 6 mos to 12 yrs	38	r, p, om, ac, mc (18 d)	80	Ciprodex: 4dr bid x 7 d versus AugmentinES-600: po bid × 10 d	Ciprodex: 74% (23/39) Augmentin: 55% (16/29)	Ciprodex: 85% (33/39) Augmentin: 59% (24/41)

r indicates randomized; p, prospective; om, observer-masked; ac, active-controlled; mc, multi-center; dr, drops; bid, twice daily; tid, 3 times daily; po, orally; ciprodex, ciprofloxacin 0.3%/dexamethasone 0.1%; ciloxan, ciprofloxacin 0.3%; cortisporin, neomycin/polymyxin B/hydrocortisone; floxin, ofloxacin 0.3%; augmentinES600, amoxicillin 600 mg /42.9 mg clavulanic acid; pp, per protocol.

In the first trial,[32] 909 patients were randomized (1:1:1) at 53 sites to receive ciprofloxacin/dexamethasone, ciprofloxacin 0.3%, or neomycin/polymyxin B/hydrocortisone. The mean age was 20.9 years (range, 1–88 years). In the second trial,[32,33] 468 patients were randomized (1:1) at 27 sites to receive either ciprofloxacin/dexamethasone or neomycin/polymyxin B/hydrocortisone (mean age 22.8 years, range, 1–90 years).

Clinical cures in these 2 trials for ciprofloxacin/dexamethasone were 87% and 94%, respectively, versus 84% and 89% for neomycin/polymyxin B/hydrocortisone, respectively. Microbiological eradication rates were 86% and 92% for ciprofloxacin/dexamethasone, respectively, versus 84% and 89% for neomycin/polymyxin B/hydrocortisone, respectively. Ciprofloxacin/dexamethasone was superior to neomycin/polymyxin B/hydrocortisone in eradicating *P. aeruginosa*, the major AOE pathogen (93.5% vs. 81.1%, respectively; $P = 0.03$).[33] Furthermore, ciprofloxacin/dexamethasone-treated patients had significantly less pain on days 2 ($P = 0.02$) and 3 ($P = 0.04$) and less inflammation ($P = 0.004$) and edema ($P = 0.02$) on day 3, as assessed by investigators.[34]

Clinical Trials for AOMT

Three prospective, well-controlled, randomized, observer-masked, active-controlled, multicenter AOMT clinical trials have been conducted for ciprofloxacin/dexamethasone (Table 1).[36–38] Patients 6 months and older with AOMT of no more than 3 weeks duration were randomized to receive either ciprofloxacin/dexamethasone or a comparator. Signs and symptoms of AOMT were assessed by investigators on days 3, 8 or 11 (end of therapy), and 18 (test of cure).

In the first AOMT trial, a total of 201 patients were enrolled (1:1) at 18 sites in the United States to receive either ciprofloxacin/dexamethasone or ciprofloxacin 0.3%.[36] In the culture positive group (167 patients), the mean time to cessation of otorrhea was 4.22 days for ciprofloxacin/dexamethasone-treated patients versus 5.31 days for ciprofloxacin 0.3%-treated patients ($P = 0.004$). Patients treated with ciprofloxacin/dexamethasone exhibited superior clinical responses versus ciprofloxacin at days 3 ($P < 0.0001$) and 8 ($P < 0.05$) ans microbiologic eradication rates, 90.7% versus 79.7%, respectively.

In the second AOMT clinical trial,[37] a total of 599 patients were randomized (1:1) at 39 centers throughout the United States and Canada to receive either ciprofloxacin/dexamethasone (7 days) or ofloxacin (10 days). Clinical cures favored ciprofloxacin/dexamethasone (86%) over ofloxacin (79%), overall, and among culture positive patients, 90% versus 78.2% ($P = 0.003$), respectively. Ciprofloxacin/dexamethasone was also superior with regard to the median time to cessation of otorrhea, 4 days versus 6 days ($P = 0.02$), treatment failures, 4.4% versus 14.1% ($P = 0.002$), and microbiologic eradication, 91% versus 82% ($P = 0.0061$), respectively.

Also in the second AOMT trial,[39] a total of 90 patients had granulation tissue upon entry, 49 in the ciprofloxacin/dexamethasone arm, and 41 in the ofloxacin arm. Granulation tissue is a manifestation of robust tissue inflammatory response that might result in fibrosis and may compromise the middle ear function.[40] Ciprofloxacin/dexamethasone treatment was superior to ofloxacin in reducing granulation tissue at days 11 (81.3% vs. 56.1%, $P = 0.007$) and 18 (91.7% vs. 73.2%, $P = 0.02$).[39] The superiority of ciprofloxacin/dexamethasone in the treatment of granulation tissue was attributed to the antiinflammatory effect of dexamethasone.

The third AOMT clinical trial was conducted to evaluate the efficacy of topical ciprofloxacin/dexamethasone (7 days) versus oral amoxicillin (10 days) in the treatment of pediatric AOMT patients.[38] Ciprofloxacin/dexamethasone was superior to amoxicillin with regard to median time to cessation of otorrhea, 4.0 days versus 7.0 days, and clinical cures, 85% versus 59% ($P = 0.01$), respectively. The study was too small to demonstrate statistical significance for microbiological eradication (40 patients per arm), although the trend was in favor of ciprofloxacin/dexamethasone.

Other Clinical Trials

Giles et al reported that ciprofloxacin/dexamethasone reduces the incidence of post-tympanostomy tube otorrhea[41] versus no drug treatment. Starkweather and Friedman reported no detrimental effect of ciprofloxacin/dexamethasone on postoperative graft healing.[42] Greater caregiver satisfaction has been reported for ciprofloxacin/dexamethasone versus ofloxacin based on greater clinical cures, shorter duration of ear drainage, more otorrhea-free days, and less potential for further treatments.[43–45]

Adverse Events

In registration studies of ciprofloxacin/dexamethasone, no clinically relevant changes in hearing function were observed in 69 pediatric patients (age 4–12 years).[5] The most common adverse events in AOMT patients were ear discomfort (3.0%), ear pain (2.3%), ear residue (0.5%), irritability (0.5%), and taste perversion (0.5%). The most common adverse events in AOE patients were ear pruritus (1.5%), ear debris and superimposed infection (0.6%), ear congestion, pain, and erythema (0.4% each).[5] No specific studies have been conducted regarding cortisol suppression. Neither have specific studies been conducted for the treatment of infections due to methicillin-resistant *S. aureus*. Because use of antibacterials can be associated with fungal overgrowth, if the infection is not improved after 1 week of treatment, cultures should be obtained to guide further treatment.[5]

DISCUSSION

In 1995, the Center for Disease Control and Prevention launched a national campaign to reduce antimicrobial resistance through promotion of more appropriate antibiotic use.[46] Topical treatment of ear infections is one of the most effective ways to treat infections while reducing the potential for resistance. With topical treatment, high concentrations of antibiotic can be delivered directly to the site of infection to eradicate organisms that would be resistant to lower antibiotic concentrations attained systemically. Using high concentrations of antibiotic for a short duration of treatment, the infection is often cured with a reduced probability of resistance development. This hypothesis is supported by findings of an evidenced-based medicine review of the ear drops literature.[47]

Clinical studies have demonstrated the safety and efficacy of fluoroquinolones in the topical treatment of ear infections. Ciprofloxacin/dexamethasone was shown to be safe in studies of pediatric and adult AOE and AOMT patients. In addition, ciprofloxacin/dexamethasone proved to be more effective than formulations containing fluoroquinolone alone and older antibiotic/steroid combination products.

ACKNOWLEDGMENTS

The authors thank Heba Costandy, MD, and Beverly Loyd for assistance with preparation of the manuscript.

REFERENCES

1. Myer CM. Historical perspective on the use of otic antimicrobial agents. *Pediatric Infect Dis J*. 2001;20:98–101.
2. Roland PS, Rutka JA. *Ototoxicity*. Hamilton, Ontario: BC Decker; 2004.
3. Rohn GN, Meyerhoff WL, Wright CG. Ototoxicity of topical agents. *Otolaryngol Clin N Am*. 1993;26:747–758.
4. Morizono T, Paparella MM, Juhn SK. Ototoxicity of propylene glycol in experimental animals. *Am J. Otolaryngol*. 1980;1:393–399.
5. CIPRODEX® Sterile otic suspension. Available at: http://a1020.g.akamai.net/7/1020/2226/66c99f43327aaf/ecatalog.alcon.com/pi/CiprodexOticSusp_us_en.pdf. Accessed April 16, 2007.

6. Cipro® HC Otic NDA –20805 approval. Available at: http://www.fda.gov/cder/foi/nda/98/20805-mr.pdf. Accessed April 17, 2007.
7. FLOXIN® Otic prescribing information. Available at: http://www.floxinotic.com. Accessed April 17, 2007.
8. Bluestone CD, Klein, J.O. *Otitis Media in Infants and Children.* 3rd ed. Philadelphia, PA: WB Saunders Company; 2001:59.
9. Roland PS, Stroman DW. Microbiology of acute otitis externa. *Laryngoscope*. 2002;112:1166–1177.
10. Hannley M, Denneny JC III, Holzer SS. Use of ototopical antibiotics in treating 3 common ear diseases. *Otolaryngol Head Neck Surg*. 2000;122:934–940.
11. Rosenfeld RM, Brown L, Cannon CR, et al. American Academy of Otolaryngology-Head Neck Surgery Foundation. Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg*. 2006;134(suppl 4):S4–S23.
12. Issacson G, Rosenfeld RM. Care of the child with tympanostomy tubes. *Pediatric Clin North Am*. 1996;43:1183–1193.
13. Hochman J, Blakley B, Abdoh A, et al. Post-tympanostomy tube otorrhea: a meta-analysis. *Otolaryngol Head Neck Surg*. 2006;135:8–11.
14. Roland PS, Parry DA, Stroman DW. Microbiology of acute otitis media with tympanostomy tubes. *Otolaryngol Head Neck Surg*. 2005;133:585–595.
15. Spektor Z, Jasek MC, Jasheway D, et al. Pharmacokinetics of CIPRODEX® otic in pediatric and adolescent patients. *Int J Pediatr Otorhinolaryngol*. 2008;72:97–102.
16. Claes J, Govaerts PJ, Van de Heyning Ph, et al. Lack of ciprofloxacin ototoxicity after repeated ototopical application. *Antimicrob Agents Chemother*. 1991;35:1014–1016.
17. Ikiz AO, Serbetcioglu B, Guneri EA, et al. Investigation of topical ciprofloxacin ototoxicity in guinea pigs. *Acta Otolaryngol*. 1998;118:808–812.
18. Brownlee RE, Hulka GF, Prazma J, et al. Ciprofloxacin use as a topical otic preparation. *Arch Otolaryngol Head Neck Surg*. 1992;118:392–396.
19. Becvaroski Z, Kartush JM, Bojrab DI. Intratympanic ciprofloxacin and the human labyrinthine sampling model. *Laryngoscope*. 2002;112:686–688.
20. Thomas SP, Buckland JR, Rhys-Williams R. Potential ototoxicity from triamcinolone, neomycin, gramicidin and nystatin (Tri-Adcortyl™) cream. *J Laryngology Otology*. 2005;119:48–50.
21. Halama AR, Wright CG, Meyerhoff WL. Ototoxicity of an ototopical preparation-experimental results and clinical facts. *Acta Otorhinolaryngologica Belg*. 1991;45:279–282.
22. Bath A, Walsh RM, Bance ML, et al. Ototoxicity of topical gentamicin preparations. *Laryngoscope*. 1999;109(7 Pt 1):1088–1093.
23. Morizono T. Toxicity of ototopical drugs: animal modeling. *Ann Otol Rhinol Laryngol*. 1990;99:42–45.
24. Spandow O. Are glucocorticoids in ear drops ototoxic? *Acta Otolaryngol.* 1992;Suppl 493:89–91.
25. Kaplan DM, James A, Thorp MA, et al. Effects of middle ear application of Cipro HC otic suspension in an animal model. *J Otolaryngology*. 2004;33:160–164.
26. Kaufman RS. The use of tissue adhesive (isobutyl cyanoacrylate) and topical steroid (0.1 percent dexamethasone) in experimental tympanoplasty. *Laryngoscope*. 1974;84:793–804.
27. Oshima T, Abe S, Tsutsui Y, et al. Influences of hydrocortisone 17-butyrate 21-propionate on the visual and the auditory organs. *J Toxicol Sci*. 1981;6(suppl):141–158.
28. Guzman J, Ruiz J, Eshraghi AA, et al. Triamcinolone acetonide protects auditory hair cells from 4-hydroxy-2,3-nonenal (HNE) ototoxicity in vitro. *Acta Otolaryngol*. 2006;126:685–690.
29. Russell PT, Church CA, Jinn TH, et al. Effects of common topical preparations on the morphology of isolated cochlear outer hair cells. *Acta Otolaryngol*. 2001;121:135–139.
30. Shefelbine SE, Young LJ, Antonelli PJ. Mitigation of hearing loss from semi-circular canal transaction in pseudomonas otitis media with ciprofloxacin-dexamethasone irrigation. *Otol Neurotol*. 2006;27:265–269.
31. Hebda PA, Yuksel S, Dohar JE. Effects of ciprofloxacin-dexamethasone on myringotomy wound healing. *Laryngoscope*. 2007;117:522–528.
32. Ciprodex (Ciprofloxacin & Dexamethasone) Sterile Otic Solution. Application No: 021537. Medical Review(s). Available at: http://www.fda.gov/cder/foi/nda/2003/021537_Ciprodex_medr.PDF?bcsi_scan_0FB272F24E6BDA79=0&bcsi_scan_filename=021537_Ciprodex_medr.PDF. Accessed May 14, 2007.
33. Roland PS, Pien FD, Schultz CC, et al. Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. *Curr Med Res Opin*. 2004;20:1175–1183.
34. Roland PS, Younis R, Wall GM. A comparison of ciprofloxacin/dexamethasone and neomycin/polymyxin/hydrocortisone for otitis externa pain. *Adv Ther*. 2007;24:671–675.
35. Rahman A, Rizwan S, Waycaster C, et al. Pooled analysis of two clinical trials comparing the clinical outcomes of topical ciprofloxacin/dexamethasone otic suspension and polymyxin B/neomycin/hydrocortisone otic suspension for the treatment of acute otitis externa in adults and children. *Clin Ther*. 2007;29:1950–1956.
36. Roland PS, Anon JB, Moe RD, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tube. *Laryngoscope*. 2003;113:2116–2122.
37. Roland PS, Kreisler LS, Reese B, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tube. *Pediatrics*. 2004;113:e40–e46.
38. Dohar J, Giles W, Roland PS, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tube. *Pediatrics*. 2006;118:e561–e569.
39. Roland PS, Dohar JE, Lanier BJ, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of granulation tissue children with acute otitis media with otorrhea through tympanostomy tubes. *Otolaryngol Head Neck Surg*. 2004;130:736–741.
40. Wright CG, Meyerhof WL. Pathology of otitis media. *Ann Otol Rhinol Laryngol Suppl*. 1994;163:24–26.
41. Giles W, Dohar J, Iverson K, et al. Ciprofloxacin/dexamethasone drops decrease the incidence of physician and patient outcomes of otorrhea after tube placement. *Int J Pediatr Otorhinolaryngol*. 2007;71:747–756.
42. Starkweather A, Friedman RA. Effect of Ciprodex on graft healing in tympanoplasty. *Adv Ther*. 2007;24:427–435.
43. Waycaster C, Cockrum P, Reese B, et al. Treatment of acute otitis media in children with tympanostomy tubes: a caregiver's perspective. *Pharm Ther*. 2004;29:721–722, 729–730.
44. Roland PS, Pontius A, Wall GM, et al. A cost threshold analysis of ciprofloxacin-dexamethasone versus ofloxacin for acute otitis media in pediatric patients with tympanostomy tubes. *Clin Ther*. 2004;26:1168–1178.
45. Roland PS, Waycaster CR, Wall GM, et al. An economic evaluation of two ototopical treatments for acute otitis media in tympanostomy tube patients. *Value Health*. 2006;9:219–226.
46. Center for Disease Control and Prevention. Get smart: know when antibiotics work. April 21, 2006. Available at: http://www.cdc.gov/drugresistance/community/anitbiotic-resistance.htm. Accessed April 12, 2007.
47. Weber PC, Roland PS, Hannley M, et al. The development of antibiotic resistant organisms with the use of ototopical medications. *Otolaryngol Head Neck Surg*. 2004;130(suppl 3):S89–S94.