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

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ABSTRACT

Objective: This study aimed to compare the clinical outcome of patients receiving topical ciprofloxacin 0.3%/dexamethasone 0.1% (CD) otic suspension with that of those receiving polymyxin B/neomycin/hydrocortisone (PNH) otic suspension for the treatment of acute otitis externa (AOE).

Methods: Data from 2 institutional review board–approved, multicenter, observer-masked, parallel-group, randomized, noninferiority clinical trials conducted at 76 institutions across the United States between April 1998 and July 1999 were pooled together for this analysis. Patients ≥1 year of age diagnosed with AOE were considered for inclusion in the studies. Patients with AOE >4 weeks' duration, a perforated tympanic membrane, chronic suppurative otitis media, or use of either antibiotics or steroids within the previous 7 days were excluded from the studies. Patients were randomly assigned to receive CD or PNH for 7 days. CD was administered as 3 drops in children and 4 drops in patients ≥12 years of age BID. PNH was administered as 3 drops in children and 4 drops in patients ≥12 years of age TID. The clinical investigators were blinded to treatment assignment. Due to the different dosing regimens, patients were not blinded, but they also were not directly informed of their treatment assignments. Otic inflammation, tenderness, edema, and discharge were clinically assessed on days 3, 8, and 18 of the studies. Otic inflammation and edema were evaluated using a 4-point scale (none = 0; mild = 1; moderate = 2; and severe = 3). Otic tenderness and discharge were rated on a binomial scale (absent = 0 and present = 1). The clinical assessments were aggregated into a 9-point composite clinical scale (range, 0–8) to compare baseline severity between groups. For the final outcomes assessment in this study, the aggregated clinical scores were dichotomized into cured (0) versus noncured (>0) and analyzed using a Kaplan-Meier survival technique. A log-rank test was used to compare the cure curves between treatment groups. Kaplan-Meier summary statistics provide the mean and median times to cure, and the mean times to cure for the 25th and 75th patient quartiles. Tolerability was assessed by monitoring patients for adverse events at each visit.

Results: Data from 1072 patients (1242 ears) were included in the analysis (CD, 537 patients; PNH, 535 patients). Baseline AOE severity and demographic characteristics were similar between the 2 treatment groups. The mean patient age was 21.7 and 22.0 years in the CD and PNH groups, respectively. Both groups were similar with respect to sex, with 50.7% and 53.5% females in the CD and PNH groups, respectively. The racial composition was predominately white (88.6% vs 84.9% in the CD and PNH groups, respectively). The log-rank test revealed a significant difference in the AOE cure curves between the CD and PNH groups ($P = 0.038$). The proportions cured in the AOE at-risk groups at the day-3, -8, and -18 assessments in the CD and PNH treatment groups were 0.14 and 0.10, 0.75 and 0.72, and 0.98 and 0.97, respectively. The Kaplan-Meier summary statistics indicated that the mean time to cure was 0.6 day less with CD com-

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pared with PNH (9.7 vs 10.3 days). Treatment-related adverse event rates were similar between the 2 groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%).

Conclusion: These data from 2 previous studies suggest that time to cure was significantly less with CD compared with PNH in patients with AOE. (*Clin Ther.* 2007;29:1950–1956) Copyright © 2007 Excerpta Medica, Inc.

Key words: otitis externa, drug therapy, antibacterial agents, anti-inflammatory agents, ciprofloxacin, polymyxin B, administration, topical, treatment outcome.

INTRODUCTION

Acute otitis externa (AOE), also known as "swimmer's ear" or "tropical ear," is a infection and/or inflammation of the external ear canal.[1] The 2 most characteristic presenting symptoms of otitis externa are otic discomfort and edema.[2] The ear discomfort can range from pruritus to severe pain (otalgia) that is exacerbated by motion of the ear, including chewing. If inflammation causes sufficient swelling to occlude the external auditory canal, the patient may also experience aural fullness and loss of hearing.[3]

Each year AOE affects 1 in 250 within the US population and ~10% of people experience AOE at some point in their lifetimes.[2] Risk factors for AOE include high humidity, warm temperatures, and exposure to water with high bacterial counts.[4] Nearly all cases (98%) of AOE in North America are caused by bacteria.[2] The signs and symptoms of otitis externa with a bacterial etiology tend to be more intense than in other forms of the disease.[5]

Topical antibacterial therapy, either alone or in combination with a steroid, is considered the standard of care for AOE.[2] Although the evidence is contradictory, it is generally thought that the addition of a topical steroid facilitates the recovery process by decreasing the inflammation and edema thus resolving symptoms more quickly.[6] In one study,[1] otitis externa was found to be sufficiently disabling to interrupt activities of daily living in 36% of patients for a median duration of 4 days, with 21% requiring bed rest. If otitis externa is not optimally treated, especially in immunocompromised patients, a potentially life-threatening infection can spread to the surrounding tissues.[6]

Treatment recommendations vary somewhat across the United States, but it is most commonly recommended that ear drops be given for 3 days beyond the cessation of symptoms (typically 5–7 days).[3] However, in patients with more severe infections, 10 to 14 days of treatment may be required.[7] Established treatments, including ear drops containing a combination of neomycin/polymyxin B/hydrocortisone, have been found to be effective in the treatment of AOE. However, ear drops, including fluoroquinolones that contain ciprofloxacin or ofloxacin, are popular alternative treatments for AOE based on their excellent coverage against gram-positive and gram-negative organisms and an improved safety profile over the aminoglycosides.[3]

The incidence of hypersensitivity reactions to neomycin-containing ear drops has been reported to be as high as 13%, whereas such reactions to fluoroquinolones have been reported to be rare.[8,9] Also, ototoxicity is not a concern with fluoroquinolones, whereas aminoglycosides have the potential to damage the inner ear when the tympanic membrane is perforated.[10–12] In a randomized study by Roland et al[13] in 468 patients with AOE aged 1 to 90 years, ciprofloxacin 0.3%/dexamethasone 0.1% (CD) 3 or 4 drops BID for 7 days was well tolerated, with no serious adverse events reported, although 2 patients discontinued treatment because of superimposed infections requiring other treatments. One patient discontinued treatment because of tympanic perforations, but it was deemed unrelated to the therapy.

The objective of this study was to compare the clinical outcomes of topical AOE therapy in patients treated with either CD otic suspension or polymyxin B 10,000 IU · mL^{-1}/neomycin 0.35%/hydrocortisone 1.0% (PNH) otic suspension and to determine whether either therapy offers a clinical advantage over the other.

MATERIALS AND METHODS

The data for this study were obtained from 2 institutional review board–approved, multicenter, observer-masked, parallel-group, randomized, noninferiority clinical trials comparing CD to PNH conducted at 76 institutions across the United States between April 1998 and July 1999.[13,14] These 2 trials were used for CD product registration with the US Food and Drug Administration (FDA).

Inclusion and Exclusion Criteria

Male and female patients >1 year of age with a clinical diagnosis of AOE were considered eligible for the studies. Patients were excluded if they had any of the following conditions: AOE >4 weeks' duration, a perforated tympanic membrane, chronic suppurative otitis media, malignant otitis externa, abnormality of the external auditory canal, use of antibiotics or steroids within the 7 days before the study, or were pregnant or breastfeeding. All patients provided written informed consent to participate.

Study Drug Administration

In patients presenting with a unilateral otic infection, only the affected ear was treated. In patients presenting with bilateral infection, both ears were treated. Patients presenting with a unilateral ear infection who subsequently developed an infection in the contralateral ear were treated in both ears.

Patients enrolled in the studies were randomly assigned, using a randomization code provided by Alcon Biostatistics Department, to receive CD or PNH for 7 days. CD was administered as 3 drops in children and 4 drops in patients ≥12 years of age BID. PNH was administered as 3 drops in children and 4 drops in patients ≥12 years of age TID. The clinical investigators were blinded to treatment assignment. Due to the different dosing regimens, patients were not blinded, but they also were not directly informed of their treatment assignment.

Primary Outcomes

In both clinical trials, AOE outcomes were assessed on 4 clinical parameters: otic inflammation, edema, pain, and discharge. Inflammation and edema were evaluated using the following 4-point scale: none = 0; mild = 1; moderate = 2; and severe = 3. Ear tenderness and otic discharge were rated on a binomial scale (absent = 0 and present = 1). Clinical parameters were assessed at baseline and day-3, -8, and -18 (test-of-cure) visits. Since all of the aforementioned clinical parameters represent unique facets of AOE, the clinical assessments were summed to create a composite clinical score with a potential range of 0 to 8. The composite clinical score was then transformed into a dichotomized scale of cured versus not cured. *Cured* was defined as the absence of all presenting signs and symptoms, that is, a composite clinical score of 0 while *not cured* was defined as any composite score >0. The dichotomized scale, cured versus not cured, was used in the Kaplan-Meier survival analysis to compare the cure rates between CD and PNH. Tolerability was assessed by monitoring patients for adverse events at each visit. All adverse events reported by the patients or observed by the clinical investigators were documented and subsequently classified as either related or unrelated to the study medications.

Compliance was assessed using patient diaries and direct questioning, but was not formally assessed.

Statistical Analysis

As these 2 trials were nearly identical in their design, the data were pooled to increase statistical power to show a difference between the 2 active comparators. Alpha was set at 0.05 for statistical significance.

Statistical analysis was conducted using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina). The categorical demographic variables of sex and race were compared between treatment groups using Pearson's χ^2 statistic. Patient age was compared between treatment groups using an independent samples t test. Baseline AOE clinical composite scores was compared between treatment groups using a t test for independent samples. The CD and PNH time to cure were compared using a Kaplan-Meier survival analysis with a log-rank statistic to test for differences in the event time survival functions between the 2 groups.[15,16] The null hypotheses for the log-rank test states that the time-to-cure distributions are similar between the CD and PNH groups. The alternative hypothesis states that the time-to-cure distributions are different between groups.

RESULTS

Baseline Assessment

All totaled, 1072 patients were enrolled in the clinical trials. Five hundred thirty-seven patients were assigned to the CD treatment group and 535 patients were assigned to the PNH group. Of the 537 patients assigned to the CD group, 452 presented with unilateral AOE while 85 presented with bilateral AOE or developed AOE in the contralateral ear over the course of the study. Of the 535 patients assigned to the PNH group, 450 presented with unilateral AOE while 85 presented with bilateral AOE or developed AOE in the contralateral ear over the course of the study. This sample of 1072 AOE patients (1242 ears) represents the pooled intent-to-treat data sets from both clinical trials.

Baseline analysis revealed no statistical differences between the 2 treatment groups in AOE severity or demographic parameters. With respect to the CD and PNH groups, the mean patient ages were 21.7 and 22.0 years. Both groups were similar with respect to sex at 50.7% and 53.5% female, respectively. The racial composition was predominately white, at 88.6% and 84.9%, respectively. Baseline composite clinical severity was also similar (both, 5.3) (**Table I**).

Outcomes Assessment

The Kaplan-Meier log-rank test indicated a significant difference in the cure curves between the CD and PNH treatment groups ($P = 0.038$). The proportions cured in the AOE at-risk populations at the day-3, -8, and -18 assessments between the CD and PNH treatment groups were 0.14 and 0.10; 0.75 and 0.72; and 0.98 and 0.97, respectively. The **figure** contrasts the cure curves of the CD and PNH groups and illustrates the higher cure rates in the CD group relative to the PNH group.

The Kaplan-Meier summary statistics revealed that the mean time to cure was 0.6 day shorter in the CD group compared with that in the PNH group (9.7 vs 10.3 days). The median time to cure and time necessary to cure 25% of the patients was 8 days in the 2 groups. However, the estimated time needed to cure 75% of the AOE patients was 8 days in the CD group compared with 18 days in the PNH group (**Table II**).

Treatment-related adverse event rates were similar between the 2 groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%).

DISCUSSION

These results suggest that AOE patients treated with CD achieve cure quicker than those treated with PNH. Kaplan-Meier analysis suggested that patients who received CD were cured by a mean of 0.6 day sooner than those who received PNH. Although the median time to cure was 8 days in the CD and PNH groups, the similarity in the median times was simply a consequence of only 3 clinical assessment points, with the median point occurring at day 8.

Also worthy of mention are the time estimates necessary to achieve a 75% cure rate. Based on each treatment group's survival function, the time necessary to achieve a 75% cure rate in the PNH group was 18 days compared with 8 days in the CD group. This faster rate represents further evidence that patients who re-

Table I. Baseline demographic and clinical characteristics of the study patients.*

Treatment	CD (n = 537)	PNH (n = 535)	All Patients (N = 1072)
Age, mean (SD), y	21.66 (16.88)	21.98 (17.50)	21.82 (17.19)
Sex, no. (%)			
Female	272 (50.65)	286 (53.46)	558 (52.05)
Male	265 (49.35)	249 (46.54)	514 (47.95)
Race, no. (%)			
White	476 (88.64)	454 (84.86)	930 (86.75)
Black	19 (3.54)	24 (4.49)	43 (4.01)
Asian	8 (1.49)	12 (2.24)	20 (1.87)
Other	34 (6.33)	45 (8.41)	79 (7.37)
Clinical composite score of AOE†	5.27 (1.26)	5.25 (1.22)	5.26 (1.24)

CD = ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension; PNH = polymyxin B/neomycin/hydrocortisone otic suspension; AOE = acute otitis externa.

*No significant between-group differences were found.

† Clinical composite score: range, 0 to 8.

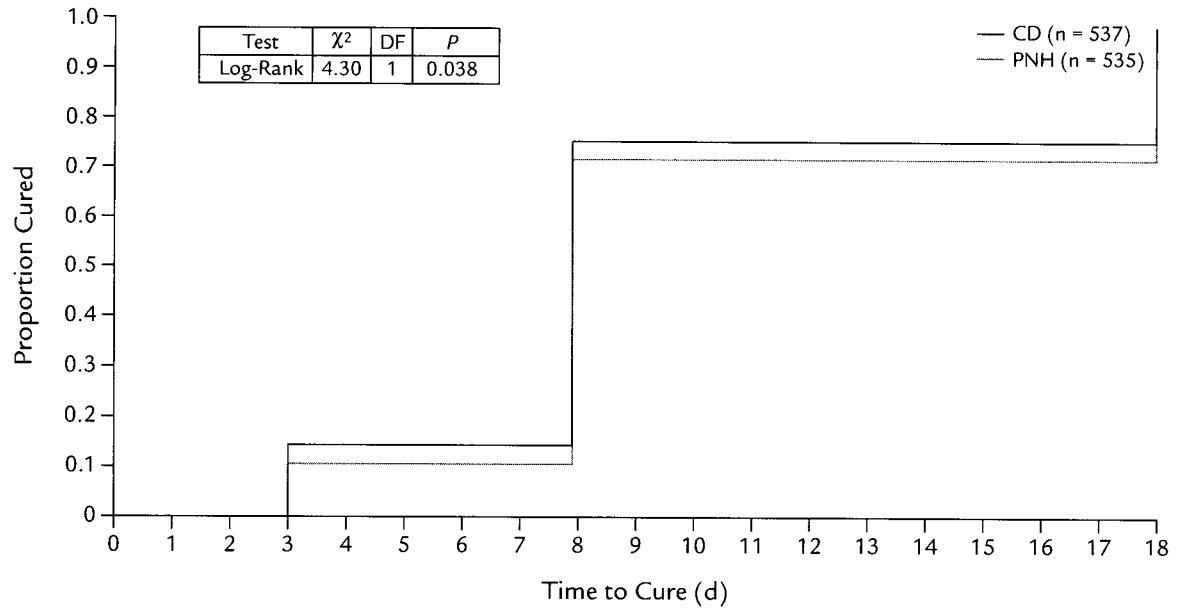

Figure. Acute otitis externa cure curves by treatment group. CD = ciprofloxacin 0.3%/dexamethasone 0.1%; PNH = polymyxin B/neomycin/hydrocortisone.

Table II. Outcome measures with 7 days of treatment with ciprofloxacin 0.3%/dexamethasone 0.1% (CD) otic suspension or polymyxin B/neomycin/hydrocortisone (PNH) otic suspension in patients with acute otitis externa.

Outcome Measure	CD (n = 537)	PNH (n = 535)	All Patients (N = 1072)
Cured, no. (%)	527 (98.14)	512 (95.70)	1039 (96.92)
Censored, no. (%)	95 (17.69)	108 (20.19)	203 (18.94)
Time to cure, d			
Mean (SD)	9.7 (0.2)	10.3 (0.2)	10.0 (0.1)
Median	8	8	-
25% Cure time	8	8	-
75% Cure time	8	18	-

ceived CD experienced faster resolution of their AOE signs and symptoms compared with those who received PNH.

There are pharmacologic bases for the different cure rates observed between the 2 treatment groups. First, corticosteroid potency was a likely factor influencing the cure rates of the respective treatment groups and thus contributing to the treatment differences. Although both hydrocortisone and dexamethasone are classified as low-potency topical corticosteroids and the concentration of hydrocortisone in PNH is 10-fold that of dexamethasone in CD, dexamethasone is ~30-fold more potent than hydrocortisone.[2,17] Even when considering the 10-fold concentration difference between hydrocortisone 1.0% in PNH and dexamethasone 0.1% in CD, the anti-inflammatory advantage still resides with CD due to the greater potency of dexamethasone. Second, growing evidence suggests that the pathogens most responsible for AOE are becoming less sensitive to neomycin and polymyxin B.[18–21] Since 1945, most microbiologic studies of AOE have identified *Pseudomonas aeruginosa* as the primary

pathogen, with incidences ranging from 12% to 80%, and indeed, the most frequently isolated bacteria from recent large-scale AOE studies (1998–2000) of 2048 ears in the United States was *P aeruginosa* (38%).[18] As early as 1996, Dohar et al[19] noted in a prospective study in 231 children seen in the outpatient Pediatric Otolaryngology Department at Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, a reduction in the sensitivity of *P aeruginosa* to neomycin and polymyxin B. This reduced sensitivity was reported again in 2001 by Jacobus et al[20] and in 2004 by Cantrell et al.[21] Fluoroquinolones are not ototoxic and are effective against *Staphylococcus aureus* and *P aeruginosa*.[13,14] The incidence of fluoroquinolone-resistant *Pseudomonas* in otitis externa is low, and hypersensitivity is quite rare.[22] Consequently, it is also possible that differences in the antimicrobial efficacy of CD, containing ciprofloxacin, and PNH, containing neomycin and polymyxin B, accounted for the observed differences in cure rates. Given the short course of therapy, the relative efficacy of the alternative ototopical therapies, and the limited number (3) of assessment visits, it is noteworthy that any difference in outcome was uncovered. However, given the results, one must consider whether daily assessment of patients' clinical signs and symptoms would have revealed a mean time to cure difference larger than the 0.6-day estimate established by the Kaplan-Meier analysis.

Future research should assess the potential economic impact of the differences between CD and PNH in the treatment of AOE. Faster time to cure may initiate a cascade of events resulting in considerable economic benefits.

Study Limitations

A placebo arm was not included due to clinical and ethical considerations, as it was not possible to incorporate such a group into an active, infectious, and acutely painful condition such as AOE. The number of clinical assessments is a potential limitation to this study as there was no clinical assessment between the day-8 and -18 visits. It is uncertain whether the inclusion of additional assessments between days 8 and 18 would have influenced the results considering that the CD treatment group exhibited a higher proportion cured relative to PNH at all study assessment times. Another limitation is related to difficulty in interpretation or generalizability of the results because the study population may be different from the typical clinical population. However, given the inclusion and exclusion criteria of the 2 pooled AOE studies, we believe that the study samples were representative of typical patients with AOE. Also, participating in a trial may influence the results due to an inherent selection bias; that is, patients who participate in clinical trials may somehow be nonrepresentative of the general clinical population of interest. Lastly, the aggregation of clinical scores used to establish clinical severity at the baseline assessment has never been validated.

CONCLUSION

These data from 2 previous studies suggest that time to cure was significantly less with CD compared with PNH in these patients with AOE.

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