A Comparative Study of Two Treatment Regimens of Oral Suspension Cefprozil: Five Days Versus Ten Days in the Treatment of Acute Otitis Media
Study AI414-155

STUDY SUMMARY
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Title: A Comparative Study of Two Treatment Regimens of Oral Suspension Cefprozil: Five Days Versus Ten Days in the Treatment of Acute Otitis Media

Investigator - Location of Trial: Multicenter-10 principal investigators in the United States.
Publication: None
Study Period: 3/26/96 - 1/5/97
Clinical Phase: IV

Objective: The purpose of this study was to evaluate the safety and therapeutic response of cefprozil 30 mg/kg/day administered twice daily for 5 days in the treatment of acute otitis media; and to compare this treatment regimen with cefprozil 30 mg/kg/day administered twice daily for 10 days.

Study Design: This was a prospective, randomized, comparative, multicenter, open-label study. Patients were randomized in a 1:1 ratio to one of two treatment groups: 5 days of cefprozil 30 mg/kg/day administered twice daily or 10 days of cefprozil 30 mg/kg/day administered twice daily. Patients were stratified prior to randomization by age (<12 months versus ≥12 months), and by history of recurrent otitis media (recurrent versus not recurrent). A central telephone randomization system was used to provide the randomized treatment assignment for each patient enrolled into the study.

Number of Patients: The study was designed to accrue approximately 258 pediatric patients from 10 study sites. Actual accrual was 277 patients, 139 patients in the 5-day cefprozil treatment group and 138 patients in the 10-day treatment group. A total of 263 patients were evaluable for efficacy at the end of therapy, 157 patients in the 5-day cefprozil treatment group and 126 patients in the 10-day treatment group.

Diagnosis and Criteria for Entry: Pediatric patients between the ages of 6 months and 8 years with clinical and otoscopic findings consistent with acute otitis media were enrolled in the study.

Test Product, Dose, and Mode of Administration: Cefprozil was supplied as a powder for oral suspension in its marketed package. Investigators were instructed to reconstitute the product for suspension with distilled water as directed on the product label. Parents were instructed to administer cefprozil in two equally divided doses without regard to food intake for a treatment duration of either 5 or 10 days, depending on the randomized treatment assignment. The following drug lots were used in this study: M5E02A, M5E45A, M5E40A, M5E12B, and L5E31A.

Statistical Methods: The primary outcome analysis was based on all evaluable patients at the end of therapy. Patients were considered evaluable for efficacy if they had clinical and otoscopic findings consistent with acute otitis media, met all eligibility criteria, were 80%-120% compliant with study medication, and returned for scheduled visits. The safety analysis was based on all patients who received at least one dose of study medication.

Homogeneity of the randomization was assessed. Categorical demographic and baseline variables (risk factors and otitis media history) were compared using the Cochran-Mantel-Haenszel test of general association. Fisher's exact test was used to compare treatment groups with respect to medical history. Continuous demographic and baseline values were compared using analysis of variance (ANOVA).

Therapeutic clinical response rates at 5 days versus 10 days of therapy were compared using the Cochran-Mantel-Haenszel test for general association, adjusting for center. The Breslow-Day test was used to evaluate homogeneity of response by treatment group across centers. Two-sided 95% confidence intervals for the

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difference in therapeutic response rates between the two treatment groups were constructed using normal approximation of the binomial distribution. Therapeutic response rates were considered to be equivalent if the 95% confidence intervals for the difference between therapies was within 15%.

Otoscopic response was evaluated at each visit. The Cochran-Mantel-Haenszel test for general association was used to compare the frequency of otoscopic signs and symptoms as well as otoscopic response between the 5-day and 10-day treatment groups.

All patients who received at least one dose of study medication were included in the safety analysis. The safety evaluation included an examination of the incidence rates of adverse events for all patients who received at least one dose of study drug. The incidences of adverse events and treatment-related adverse events were assessed using Fisher's exact test when an event occurred in at least 5% of patients.

Pretreatment Characteristics: A total of 277 patients were enrolled, of which 263 were considered evaluable for efficacy at the end of therapy. Slightly more males than females were enrolled and most patients were White. The mean age was 2.45 years (min, max: 0.4, 8 years) in the 5-day treatment group and 2.66 (min, max: 0.5, 8 years) in the 10-day treatment group. Approximately 70% of the patients in both treatment groups were 3 years of age or younger. More than 50% of the patients in both groups were enrolled in day care and had siblings 8 years of age or younger in their household. Most of the patients (80%) were not considered to have recurrent otitis media. The most common presenting clinical signs and symptoms of acute otitis media were irritability, earache, ear pulling, and ear pain.

Microbiology: A total of 75 of the 139 (54%) patients treated with 5 days of cefprozil and 74 of 138 (54%) patients treated with 10 days of cefprozil underwent tympanocentesis. Forty-three (31%) of the 137 evaluable patients in the 5-day group and 57/131 (44%) patients in the 10-day group had tympanocentesis results which revealed positive bacterial cultures. For the three most frequently identified causative pathogens of otitis media, S. pneumoniae, H. influenzae, and M. catarrhalis, resistance to cefprozil (MIC ≥32 μg/mL) was demonstrated in 6 of 42 strains of S. pneumoniae and 1 of 29 strains of M. catarrhalis. All 35 isolates of H. influenzae were susceptible to cefprozil (MIC ≤8 μg/mL). The six resistant strains of S. pneumoniae were also penicillin-resistant strains (MIC ≥2 μg/mL).

Clinical Response: The results of this study are confounded by flaws in the study design, resulting in extensive antibiotic usage during the follow-up period (46% in the 5-day group and 41% in the 10-day group), tympanocentesis in only half of the patients, and scheduled evaluations at times which may bias the response rates. Several analyses were considered when determining the most appropriate way to interpret the data for patients who responded to post-treatment antimicrobial for otitis media: excluding patients who responded to additional antimicrobials for O.M. which were administered prior to the scheduled evaluation, assessing these patients as failures, or including all patients regardless of post-treatment antimicrobial use. All three analyses were based on the presence of specific signs and symptoms of otitis media and were performed for the end-of-therapy and the follow-up endpoints.

The 95% confidence interval (CI) for clinical response at the end of therapy indicated that the two treatment groups were equivalent (95% CI: -12.97, 7.309) when patients were assessed regardless of additional antibiotic use. At the end of therapy, 108 of 137 (78.8%) patients treated with 5 days of cefprozil and 95 of 126 (75.4%) patients treated with 10 days of cefprozil had a satisfactory (cured or improved) clinical response.

At the follow-up evaluation on Study Days 24-32, 97 of 134 (72.4%) patients treated with 5 days of cefprozil and 97 of 123 (78.9%) patients treated for 10 days of cefprozil had satisfactory clinical responses (95% CI: -4.369, 16.42) when patients were analyzed regardless of additional antibiotic use.

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The satisfactory clinical response rates at the end of therapy for evaluable patients analyzed regardless of their additional antibiotic use in the 5-day and 10-day groups for the most commonly isolated pathogens were as follows: 75% (15/20) and 67% (14/21), respectively, for S. pneumoniae; 80% (12/15) and 67% (12/18), respectively, for H. influenzae; and 100% (9/9) and 68% (13/19), respectively, for M. catarrhalis. No other pathogen was isolated from more than three patients in either treatment group.

Clinical response to cefprozil relative to penicillin susceptibility of S. pneumoniae was also determined. Of the 15 patients with penicillin-susceptible strains of S. pneumoniae in the 5-day treatment group, 12 (80%) achieved a satisfactory clinical response at the end of therapy. Both patients with penicillin-intermediate-resistant S. pneumoniae in the 5-day group had clinically satisfactory responses, and one of the three (33%) patients with penicillin-resistant strains of S. pneumoniae achieved a satisfactory clinical response. Of the 16 patients with penicillin-susceptible strains of S. pneumoniae in the 10-day group, 10 (63%) had a satisfactory response. One of the two patients (50%) with penicillin-intermediate-resistant strains and three of the four (75%) patients with penicillin-resistant strains of S. pneumoniae had clinically satisfactory responses in the 10-day treatment group.

Otoscopic Response: Although a greater percentage of patients in the 10-day group had resolution of otoscopic findings at the end-of-therapy assessment (55/138, 39.9%) compared with the 5-day group (25/139, 18.0%), the percentages of patients with otoscopic resolution was similar between the two treatment groups at each study visit. In each treatment group, patients showed resolution of otoscopic findings from baseline to Visit 2 (Study Day 5-7) (5-day group: 25/139 [18.0%]; 10-day group: 26/138 [18.8%]), and the percentages of patients with otoscopic resolution continued to increase at each subsequent visit (Visit 3 [Study Day 11-15] results were as follows: 5-day group: 51/139 [36.7%]; 10-day group: 55/138 [39.9%]). At the follow-up evaluation, the two treatment groups were similar with respect to otoscopic response rates (5-day group: 79/139 [56.8%]; 10-day group: 80/138 [58.0%]).

Safety: Adverse events were reported by 88% (123/139) of patients treated with 5 days of cefprozil and 84% (116/138) of those treated with 10 days. This high rate is due to investigators including signs and symptoms of infection as an adverse event. Adverse events considered to be related or possibly related to study medication were reported for 12% (16/139) and 14% (19/138) of patients in the 5-day and 10-day groups, respectively. The most common treatment-related adverse events were diarrhea and vomiting, and were reported in 6% and 4%, respectively of patients in the 5-day treatment group and 3% and 4%, respectively for patients in the 10-day treatment group.

Three patients were discontinued from treatment due to an adverse event (AE). One patient in the 5-day group was discontinued due to abnormal urine, and two patients in the 10-day group were discontinued; one due to rash and the other due to vomiting.

Two serious adverse events occurred during the study, including one patient in the 5-day cefprozil treatment group who received an overdose of cefprozil. The second patient, who was in the 10-day treatment group, developed pneumonia during the study that was not considered related to study medication. No deaths occurred during the study or the follow-up period.

Conclusion: The results of this study demonstrated that 5 days of cefprozil 30 mg/kg/day administered twice daily was equivalent to 10 days of cefprozil at the same dose for clinical responses based on the resolution of specific clinical signs and symptoms of otitis media at the end of therapy. The 10-day cefprozil treatment group had a higher otoscopic response rate at the end of therapy in patients assessed without regard to additional antibiotic use, although at the follow-up evaluation the percentage of patients with complete resolution of otoscopic abnormalities was nearly identical between treatment groups. Post-treatment antibiotic usage was high but similar in both treatment groups.

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The results of this study cannot be interpreted with confidence because of flaws in the study design. The response rates for both treatment groups were unexpectedly low, and the results of the 10-day regimen were lower than previous 10-day studies of cefprozil in the treatment of acute otitis media. The incidence of adverse events was also exceptionally high because of reporting of signs and symptoms of acute otitis media as adverse events. The incidence of treatment-related adverse events was consistent with previous studies.

Cefprozil has been shown to have comparable or superior clinical efficacy with a variety of oral antibiotics in 10-day studies, including amoxicillin/clavulanate, cefixime, and cefdinir. Several of these agents have been shown to be effective as 5-day treatment courses for acute otitis media. When considering cefprozil's microbiologic and efficacy profile, cefprozil would be expected to be effective as a 5-day treatment regimen. Further studies are necessary to confirm this hypothesis.