Study AI414-090

Title: A Multi-Investigator Randomized Trial Comparing the Efficacy of Cefprozil versus Amoxicillin/Clavulanate Potassium in the Treatment of Acute Otitis Media in Children

Investigator-Location of Trial: Multicenter European Trial - 4 principal investigators.

Publication: none


Clinical Phase: III

Objective: To evaluate the safety and efficacy of cefprozil administered orally for 10 days at 40 mg/kg/day in two divided doses versus amoxicillin/clavulanate administered orally at 40 mg/kg/day in three divided doses as treatment for acute otitis media in pediatric patients 6 months to 12 years of age.

Study Design: This open, randomized (1 cefprozil:1 amoxicillin/clavulanate) multicenter clinical trial compared the safety and efficacy of cefprozil and amoxicillin/clavulanate in pediatric patients with acute uncomplicated otitis media.

Number of Patients: A total of 361 patients, 189 male and 172 female, entered the study, 183 in the cefprozil group and 178 in the amoxicillin/clavulanate group.

Diagnosis and Criteria for Entry: Eligible patients included male and female patients from ages 6 months through 12 years with acute uncomplicated otitis media infection. Patients excluded from the study were those with chronic or suppurative otitis media, otitis media with complications, or patients with perforated tympanic membrane or tympanostomy tubes. Also excluded were patients with concomitant serious medical conditions such as renal, hepatic, or immunologic disorders. Patients could not have a history of hypersensitivity to penicillin or cephalosporin compounds.

Test Product, Dose, and Mode of Administration: Cefprozil was supplied as a powder for reconstitution into oral suspension (250 mg/5 ml) and was administered orally at 40 mg/kg/day in two equally divided doses for a recommended duration of 10 days. The maximum daily dose was 1000 mg.

Reference Therapy, Dose, and mode of Administration: Amoxicillin/clavulanate potassium was supplied as a powder for reconstitution into oral suspension (250 mg amoxicillin and 62.5 mg clavulanate acid/ per 5 ml) and was administered orally as 40 mg/kg/day divided into three equally divided doses for a recommended duration of 10 days. The maximum daily dose was 1500 mg.

Duration of Treatment: Fifty-three percent of cefprozil patients and 47% of amoxicillin/clavulanate patients completed the recommended 10 or more days of study therapy (p=0.184).

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Statistical Methods: Safety and efficacy results are based on data from all patients who received at least one dose of study medication. Efficacy analyses are based on all patients for whom a post-treatment assessment of clinical and/or bacteriologic response was available. For efficacy analyses, the "unable to determine" classification was excluded. All efficacy and safety data were listed and summary statistics tabulated for both the pooled data and each investigator. The stratified Cochran-Mantel-Haenszel test was used to compare rates with statistical adjustments made for the effect of investigators. The likelihood ratio test statistic based on Gail and Simon was used to test the null hypothesis of no qualitative treatment-by-stratum interaction. Fisher's Exact test was used to compute the unadjusted p-values for binary data and Mantel-Haenszel Chi-square Test for polychotomous data at each center. The two-way ANOVA procedure based on ranks was used for continuous variables, specifically: age, weight and height. Wilcoxon's Rank Sum test was used to analyze continuous data at each center. For analysis of data when combining all investigators, two linear models were examined. The first model (Model I) contained a treatment-by-investigator interaction term. If this interaction was not statistically significant at the 10% level of significance, then a second model (Model II) without an interaction term was analyzed. When a statistically significant pre-treatment characteristic was present and felt to be clinically important, efficacy responses were examined adjusted for the characteristic using the Cochran-Mantel-Haenszel test. For the two primary endpoints in the efficacy dataset, the difference between the response rates and the 95% confidence intervals were constructed. To compare the rates of changes in the laboratory values among patients whose testing was normal-at-baseline, the Fisher's Exact Test was used. For comparison of the baseline characteristics, a two-sided alpha level of 0.10 was used; for the efficacy and safety rates, a two-sided alpha level of 0.05 was used. All p-values have been rounded to three decimal places.

Summary of Results:
Clinical Response: A satisfactory clinical response occurred in 145 (83%) of the 174 cefprozil-treated patients, while response could not be determined for 9 patients. The clinical response was satisfactory for 147 (84%) of the 176 amoxicillin/clavulanate treated patients, and unable to be determined for 2 patients. There was no statistically significant difference between the two treatment groups with respect to clinical response (p=1.000).

Bacteriologic Response: Bacteriologic response was similar in both treatment groups. In cefprozil patients 109 (83%) were an eradicated response (presumed or documented) versus 111 (85%) of amoxicillin/clavulanate patients (p=0.734).

Middle Ear Effusion: Following completion of study therapy, middle-ear effusion remained present in 42 (23%) of the 180 cefprozil patients assessed. Middle ear effusion remained present in 33 (19%) of the 175 amoxicillin/clavulanate patients assessed.

Antimicrobial Susceptibility: From all baseline cultures, 364 pathogens were tested for susceptibility to cefprozil. Of these, 323 (89%) isolates were susceptible, 15 (4%) displayed intermediate susceptibility and 26 (7%) were resistant. The resistant bacteria included 20 Pseudomonas aeruginosa pathogens. From the baseline cultures, a total of 367 pathogens were tested for susceptibility to amoxicillin/clavulanate. Of these, 339 (92%) were susceptible, 1 (≤1%) was of intermediate susceptibility and 27 (7%) were resistant to amoxicillin/clavulanate. The resistant bacteria included 20 Pseudomonas aeruginosa pathogens.
Safety: Twenty-four (13%) of the 183 cefprozil patients reported a total of 35 adverse clinical events during the study. Thirty-six (20%) of the 178 amoxicillin/clavulanate patients reported a total of 50 adverse clinical events during the study. There was no statistically significant difference between the treatment groups although a higher incidence of adverse clinical events was observed for the amoxicillin/clavulanate group (p = 0.089). The most common adverse events in either group were those of gastrointestinal tolerance. Six (3%) patients in the cefprozil group withdrew because of adverse clinical events. Two (1%) patients in the amoxicillin/clavulanate group withdrew because of adverse clinical events. None of the 8 patients who withdrew from the study experienced any permanent sequelae. No deaths occurred in either treatment group.

Laboratory Results: Among patients with normal pre-treatment laboratory test results, none of the cefprozil patients and 1 amoxicillin/clavulanate patient developed a clinically relevant laboratory abnormality during or following study treatment. Of the patients who entered the study with an abnormal pre-treatment laboratory test, 0 cefprozil patients and 1 amoxicillin/clavulanate patients had clinically relevant changes in during- or post-treatment tests. No patients were discontinued from the study due to abnormal laboratory test results.

Conclusion: A satisfactory clinical response (83%) in patients treated with cefprozil was similar to the satisfactory clinical response (84%) of patients treated with amoxicillin/clavulanate for acute otitis media. Pediatric patients treated with cefprozil had a lower rate of adverse clinical events (13%) compared to patients treated with amoxicillin/clavulanate (20%), although this was not statistically significant. In summary, this study demonstrated the efficacy and safety of cefprozil administered as suspension (40 mg/kg/day) to treat acute otitis media.