SYNOPSIS CLINICAL STUDY REPORT

Study ai 414-116:

Study title: A Comparative Trial of Cefprozil versus Erythromycin in the Treatment of Mild to Moderate Skin and Skin Structure Infections.

Product: Cefprozil oral tablets and suspension.

Study Design: Multi-center, open-label, randomized, comparative study.

Number of sites: The study was carried out in eight centers and the number of patients enrolled at each center varied.

Objective: The purpose of the study was to evaluate the efficacy, safety, and tolerability of cefprozil given once daily for ten days in comparison with erythromycin at its recommended dosage four times daily for ten days in adults and children with skin and skin structure infections.

Treatment design:

Patients with mild to moderate skin and skin structure infections and who met all other entry criteria were enrolled and randomly assigned to receive either cefprozil or erythromycin.

Cefprozil was administered orally for ten days according to one of the following regimens:
- 500 mg (two 250 tablets) once daily for patients weighing at least 25 kg, or,
- 20 mg/kg once daily for those weighing less than 25 kg.

Patients randomized to erythromycin received one of the following orally for ten days:
400 mg (one 400 mg tablet) q.i.d. (1600 mg/day) for those weighing more than 100 lbs, or,
-30 mg/kg/day of E.E.S (erythromycin ethylsuccinate) Granules in four divided doses for patients weighing 100 lbs. or less.

**Duration:** Ten days treatment followed by 14-18 days of follow-up.

**Inclusion criteria:**
- Males and females two years of age or older were eligible. Females of child-bearing potential had a negative pregnancy test result prior to enrollment and were required to use an approved method of contraception during the study.
- Patients had signs and symptoms consistent with mild to moderate skin or skin structure infections such as pyoderma (including impetigo), cellulitis, wound infections, furuncles, and carbuncles.
- Patients signed informed consent documents prior to receiving study medication. In the case of minors, the documents were signed by a parent or guardian.

**Exclusion criteria**
- A clear history of hypersensitivity to a cephalosporin or penicillin compound or erythromycin.
- Pregnancy or lactation.
- Likely to receive other antimicrobial drugs concomitantly.
- A history of any of the following: malabsorption syndromes, other gastrointestinal disturbances, renal insufficiency, current hepatic disease such as acute hepatitis, cirrhosis of the liver or abnormal liver function tests.
- Infection judged by the investigator to be too severe for oral antibiotic therapy (i.e. decubitus ulcer).
- Receipt of a long-acting parenteral penicillin within two weeks prior to enrollment.
- Previous enrollment in this study.
- Previous receipt of cefprozil.

**Size of the studied population:** A total of 223 patients with mild to moderate skin and skin structure infections and who met all other entry criteria were enrolled, 110 of whom were randomly assigned to receive cefprozil (age ranged from 1-88 years: among them 26 patients had an age between 0 and 10 years and 10 an age between 11 and 20 years) and 113 assigned to receive erythromycin (age ranged from 2-87 years: among them 28 patients had an age between 2 and 10 years and 4 an age between 11 and 20 years). Two cefprozil-randomized patients never received study drug (patient’s decisions). The 221 patients who took at least one dose of study medication comprise the study population for this report. Specific measurements and observations were made as required by the study protocol to provide data on which the analyses of efficacy, safety, and tolerability were made.

**Patients Evaluable:** Clinical Efficacy: 87 cefprozil, 78 E.E.S. Bacteriologic Efficacy: 38 cefprozil, 59 E.E.S (secondary analysis---60 cefprozil, 59 E.E.S.)
Statistical Methods:

The comparability of the cefprozil and E. E.S. treatment groups with respect to patient demographic characteristics at baseline was assessed for all patients who took study medication. These characteristics include age, sex, and race. The Cochran-Mantel-Haenszel test stratified by study site was used to compare patients' distribution, and a two-way analysis of variance with study drug and study site as the main effects was used to compare the ages in the two treatment groups.

Results:

Efficacy:

Clinical efficacy: Only patients who were entirely free of signs of infection were considered cured.

Bacteriological efficacy: comparisons were based on the results of culture and susceptibility testing done on specimens obtained from the sites of infection. Clinical and bacteriologic efficacy were assessed separately under intent-to-treat format. With the exception of two patients with Group A beta-hemolytic Streptococci, the pre-treatment causative pathogens of all the cefprozil patients evaluable for bacteriologic efficacy were Staphylococci. This resulted mainly from the resistance of Gram negative pathogens to E.E.S., which excluded these cefprozil-treated patients from analysis. No statistically significant differences in clinical or bacteriologic efficacy were found. Clinical recurrence rates were likewise not significantly different.

Safety and Tolerability: Overall adverse events profiles of cefprozil and E.E.S. were similar in frequency, severity, and relationship to study drug administration. Two (2) cefprozil and five (5) E.E.S. patients were dropped due to intolerable adverse events. Fewer patients in the cefprozil group (16%) reported at least one (1) adverse event than in the E.E.S. group (24%). This difference, however, was not statistically significant. In addition, there were no statistically significant differences in the incidence of adverse events for any of the body system groups. The most frequent adverse events reported were diarrhea: seven (7) patients in each treatment group and abdominal pain: four (4) cefprozil and seven (7) E.E.S. patients. Gastrointestinal complaints were the most frequently reported adverse events for both groups, with ten (10) reported by cefprozil patients and fourteen (14) by E.E.S. patients. All ten (10) such events reported by cefprozil patients were mild, while of the fourteen (14) reported for E.E.S, seven (50%) were mild and seven (50%) were of moderate severity.

Conclusions: Cefprozil was as effective as E.E.S. in this study in the treatment of patients who presented to their primary care physicians with mild to moderate skin and skin structures infections. Cefprozil was better tolerated than E.E.S. in this trial as indicated by the greater frequency and severity of digestive system adverse events and of resulting early terminations. The safety profiles of the two drugs were otherwise similar.