A Randomized Double-blind Investigation of Cefroxadine (CGP 9000) versus Cephalexin in Urinary Tract Infection

Summary: A total of 64 out-patients with significant urinary tract infection were randomly allocated to treatment with cefroxadine 250 mg q.i.d. or cephalexin 500 mg q.i.d. for ten days. Urine cultures were performed before allocation to the treatment groups and on Days 0, 1, 3, 7 and 21. Twenty patients discontinued treatment prematurely because of insignificant bacteriuria on Day 0. Both drug regimes - the cefroxadine dose was half that of cephalexin - showed good activity during treatment, and no statistically significant differences were found between the two drugs. At follow-up, several relapses were found in both treatment groups. Adverse drug reactions were only reported by three patients in the cefroxadine group, and by none in the cephalexin group.


Introduction

Treatment of bacterial infections with cephalosporins has become more common, partly because of the efficacy of these antibiotics, partly because they have proved to be less toxic than earlier combination therapies, e.g. with aminoglycosides, and also because of the increasing demand for alternative agents to penicillins. Cefroxadine is a newly developed semisynthetic antibiotic (7-β-[D-2-amino-2-(1,4-cyclohexadienyl)-acetamido]-3-methoxyceph-3-em-4-carboxylic acid) with a broad spectrum of activity against gram-positive and gram-negative bacteria. Unlike most cephalosporins, cefroxadine is active when given orally. The bactericidal action of cefroxadine in vitro and in vivo is more rapid and more complete than that of cephalexin; Zak et al. (1, 2) showed cefroxadine to be two to seven times more effective in general than cephalexin in mice infected with various bacteria. The pharmacokinetics of cefroxadine and cephalexin are similar after oral administration; Bergan, Leacallon and Okkawa et al. (3-5) showed that 85-95% of the dose is eliminated renally in the active form. In view of the microbiological and pharmacokinetic properties of the two drugs, cefroxadine might be equally effective at a lower dose. The purpose of this double-blind study was to compare the efficacy and tolerability of cefroxadine (1 g per day) with that of the routine dosage of cephalexin (2 g per day) in patients with urinary tract infections (UTI).

Patients and Methods

We studied out-patients over 18 years of age with significant UTI, i.e. ≥ 10^6 bacteria per ml midstream urine, which were sensitive to cephalosporins, e.g. cephalothin. After informed consent had been obtained, the patients were randomly allocated to treatment with capsules of either cefroxadine (250 mg q.i.d.) or cephalexin (500 mg q.i.d.) for ten days. Both types of capsules presented an identical appearance. Exclusion criteria were: elevated serum creatinine, urinary diversion, stones or malformations in the urinary tract, pregnancy, immunosuppression, previous treatment with cephalosporins or inability to cooperate.

Midstream urine was taken before patient selection and on Days 0, 7 and 21. It was transported immediately to the laboratory in cooled containers. Uricult specimens - also midstream - were taken on Days 1 and 3. These samples were taken at home and sent to the laboratory; the bacterial count in the urine was determined on slides. Midstream urine was diluted and spread on blood agar for counting. Strains were identified by standard methods. Sensitivity tests were performed using the Biodisc method (6). Discs contained 30 μg cefalexin/cefoxadine. Sensitivity grouping was determined according to the cefalexin

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scheme: sensitive: zone ≥ 28 mm; intermediate: zone 17–27 mm; resistant: zone ≤ 16 mm.

Only patients who still had ≥ 10^9 bacteria per ml urine at the initiation of treatment were evaluated for efficacy. If this criterion was not fulfilled, the patient had to stop treatment. Response to treatment was defined as < 10^9 bacteria per ml urine. Clinical symptoms and possible side-effects were recorded on Days 0, 7 and 21.

Blood samples were taken on Days 0, 7 and 21 to determine haemoglobin, leukocytes, thrombocytes, serum creatinine, prothrombin and ASAT.

The statistical analyses were performed by non-parametric methods. The Bernouille-Wilcoxon procedure (7) was used to construct 95% confidence intervals; all tests were one-tailed (8). The Fisher-Irwin test (9) was used to compare frequencies. To compare the two drugs, we used the van der Waerden test for the variables distributed with no mode, the Wilcoxon test for unimodal skewed distributed variables (7) and the Gehan test (10) for variables distributed with the mode at an extreme value. All statistics used in the analyses were corrected for ties. Differences were considered statistically significant if the p value was 5% or less.

Results

A total of 64 out-patients entered the study. As seen from Table 1, 20 patients discontinued therapy after a few days’ treatment, mostly because the bacterial count on Day 0 appeared to be less than 10^9 bacteria per ml urine. The 20 patients excluded were statistically comparable with the remaining 44 patients with regard to all patient characteristics. The 22 patients in each treatment group whose treatment efficacy could be evaluated were statistically comparable with regard to the corresponding characteristics, i.e. age, sex, urine bacteriology, number of days before treatment, concomitant treatment, clinical symptoms and drop-outs (Table 2). The patient population seemed to be typical for a urological department (Table 3).

The efficacy of treatment, according to the number of patients with bacteriuria before, during and after treatment, is shown in Table 4. There was a statistically significant reduction in the number of patients with bacteriuria during treatment – Days 1, 3 and 7 – compared with Day 0 in both groups. There were no statistically significant differences in this respect between the two medications. At follow-up, ten patients in the cefroxadine group and six patients in the cephalixin group had significant bacteriuria. The difference was, however, not significant.

The total number of bacteria in each treatment group was also compared before, during and after treatment, and no statistically significant differences were found between the two drugs. A significant reduction was found in the number of bacteria from Day 0 to Day 21 for both treatment groups (p < 0.01).

The most common bacterium in this material was Escherichia coli (Table 5). The two groups were comparable initially with respect to the occurrence of E. coli and Streptococcus faecalis, but there was a statistically significant larger number of E. coli strains on Day 21 in the cefrox-