Comparative Study of Cephradine and Amoxicillin-Clavulanate in the Treatment of Recurrent Urinary Tract Infections

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Eighty-eight female patients with a history of recurrent urinary tract infections were treated according to a randomization scheme with either 1 g of cephradine every 12 h (47 patients) or 375 mg of amoxicillin-clavulanate every 8 h (41 patients) for 7 days. The treatments were equally effective (cure rates of 89% for cephradine and 88% for amoxicillin-clavulanate) and showed similar relapse rates (cephradine, 14%; amoxicillin-clavulanate, 11%). Adverse effects were similar in both groups (cephradine, 23%; amoxicillin-clavulanate, 22%).

It is often necessary to treat patients with symptomatic urinary tract infections before the susceptibility of the infecting bacteria is known. This requires knowledge of local resistance patterns and likely infecting organisms, so that an antibiotic to which resistance is unusual can be chosen. Resistance to amoxicillin among organisms causing urinary tract infections in patients attending The Royal Free Hospital is now 50%; figures for trimethoprim, sulfonamide, and cinoxacin are 28, 45, and 24%, respectively. Resistance to trimethoprim and sulfonamide and the accompanying allergic reactions have caused us to abandon their use as a “blind” treatment. Broad-spectrum antibiotics unaffected by the most common R factors are most likely to be active in vitro and clinically effective. We have carried out a comparative trial of two such compounds, cephradine and amoxicillin-clavulanate, in patients referred to the Urinary Infection Clinic at The Royal Free Hospital because of a history of recurrent attacks of symptomatic urinary tract infections, typically 4 to 10 episodes per year. Previous studies (2, 3) in such patients revealed a good immediate response to antibiotic treatment, with a substantial proportion relapsing within 1 month.

During 1987 and 1988, female patients with significant bacteriuria (≥10⁵ bacteria per ml) caused by an organism susceptible to both study drugs and with no history of allergy to β-lactam antibiotics were randomized to receive either 1 g (two 500-mg doses) of cephradine (Velosef capsules) every 12 h or 250 mg of amoxicillin and 125 mg of potassium clavulanate every 8 h each day for 7 days. Neither the patients nor the doctors knew which antibiotic was being prescribed. Asymptomatic bacteriuria was detected during routine monitoring. Patients recorded every day on a diary card the number and nature of bowel movements. Follow-up appointments were scheduled 2 weeks after the infection had been diagnosed (i.e., 1 week after the end of treatment) and 4 weeks later (6-week follow-up).

Patients were questioned about adverse effects at the 2-week follow-up, and their diary cards were analyzed. The cause-and-effect relationship between the adverse effect and the antibiotic was assessed by a physician on a scale of 1 to 5 (1, no relationship; 2, unlikely; 3, possible; 4, probable; 5, certain). Grades 3, 4, and 5 were considered drug related.

Midstream urine specimens were examined at entry to the study and at the follow-up appointments. Numbers of epithelial cells, erythrocytes, and leukocytes and the presence of bacteria were determined by microscopic examination in a counting chamber, and 0.1 ml of undiluted urine and a 1:100 dilution were cultured on cystine-lactose-electrolyte-deficient agar. Significant bacteriuria was defined as ≥10⁵ bacteria per ml, and significant pyuria was defined as ≥10 leukocytes per µl.

Bacteriological cure rates were assessed from results of culturing of midstream urine specimens obtained at the 2- and 6-week follow-ups. Relapse and reinfection were distinguished by comparing the serotypes and biotypes of any organisms isolated in significant numbers from midstream urine specimens obtained at the first or second follow-up visit with the original isolate. Some patients were started on long-term prophylaxis when the 2-week follow-up showed that the urine was clear and hence could not be evaluated at the 6-week follow-up.

Ninety-five patients were originally enrolled; assessments of clinical efficacy could only be made for 85, as 3 stopped taking the prescribed antibiotic because of adverse effects, 5 failed to return for follow-up, 1 was given another antibiotic before follow-up, and the records for 1 were lost. The patients in the two treatment groups were very similar in terms of age, incidence of antibody-coated bacteria, asymptomatic infections, pyuria, and nature of the infecting organisms (Table 1). More of those treated with amoxicillin-clavulanate had a radiological abnormality, but the difference was not statistically significant. Cure rates (Table 2) showed that the treatments were equally effective. The relapse rate was below 15% in each case. Recurrent infections (32) consisted of 18 reinfections and 14 relapses or persistent infections.

A radiological abnormality did not predict a less favorable therapeutic response.

Most infecting organisms were Escherichia coli (Table 1) with similar resistance patterns. Eighteen percent of all the isolates were resistant to trimethoprim, 33% were resistant to sulfonamide, 28% were resistant to amoxicillin, 8% were resistant to cinoxacin, and 2% were resistant to nitrofurantoin. The study protocol required that all infecting strains be susceptible to cephradine and amoxicillin-clavulanate.

Eighty-eight patients were assessed for adverse effects.

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Twenty percent of patients reported adverse effects, but only one patient taking amoxicillin-clavulanate (who experienced severe diarrhea) and two patients taking cephradine (one of whom experienced indigestion and flatulence and the other of whom experienced skin rash) cut short their therapeutic course because of side effects. Gastrointestinal disturbances were the most common adverse effects in those taking amoxicillin-clavulanate (five reports of diarrhea and two reports of nausea), and rash (three reports) or vaginal irritation (four reports) were most common for those receiving cephradine. Diary cards were returned by 20 patients (50%) who had taken amoxicillin-clavulanate and 21 patients (47%) who had taken cephradine. Of these, nine patients (45%) on amoxicillin-clavulanate reported an increased frequency of bowel movements, as compared with six patients (29%) on cephradine. This difference is not significant, perhaps because of the small numbers in each group.

The pathogens isolated were commonly resistant to amoxicillin but susceptible to amoxicillin-clavulanate. Cephradine was also active against amoxicillin-resistant strains, presumably because of its stability against TEM β-lactamase (9). As very few patients had to be excluded because of resistance, either drug can be recommended on a best-guess basis, and we have shown (Table 2) that both are suitable for the treatment of recurrent urinary tract infections. The cure rates obtained in this study were similar to those previously reported in studies involving substantial numbers of patients treated with amoxicillin-clavulanate (4, 5, 7, 8) (ranging from 99 to 71%) and oral cephalosporins (6, 10; T. Sandberg, C. Henning, O. Paulsen, and S. Iwason, Proc. 13th Int. Congr. Chemother., p. 70/74–70/76, 1984) (97 to 72%) and in other defined groups such as patients with uncomplicated or complicated infections. However, the group studied by us differed from the subjects of these studies.

The choice between cephradine and amoxicillin-clavulanate must be based on cost and acceptability to patients. In the regimens described here, cephradine was 47% more expensive than amoxicillin-clavulanate at pharmacist prices. A very important determinant for compliance is how often adverse effects occur. Adverse effects might be less frequent with a shorter course of treatment (3 or 5 days), but it has not been established that such short courses are optimally effective in the type of patient studied here. We found a marked difference in the apparent incidence of adverse effects depending on how this information was elicited. Asking “Did you have any problems with the tablets?” caused only 5 of 41 patients taking amoxicillin-clavulanate and none of 47 taking cephradine to remark on changes in bowel function. However, diary cards suggested that a higher proportion of patients experienced such changes. It is possible that the subjects who registered increased stool frequency on diary cards but gave no report of adverse effects had suffered only a mild problem. However, when acceptability to patients was judged by how many failed to complete the full course, both regimens did well.

Changes in bowel movements are unlikely to be related to alterations in bowel flora. Our previous investigation (1) showed that few major quantitative or qualitative changes occurred when volunteers took amoxicillin-clavulanate or cephradine for 1 week.

In conclusion, our findings suggest that both cephradine and amoxicillin-clavulanate are excellent choices for the treatment of recurrent urinary tract infections. Our data suggest that cephradine may be associated with fewer physiological upsets to patients.

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### TABLE 2. Cure rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. cured/no. in group (%) at wk: 2 6</th>
<th>Relapse rate (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>35/40 (88) / 37/40 (92)</td>
<td>11</td>
</tr>
<tr>
<td>Cephradine</td>
<td>40/45 (89) / 39/45 (87)</td>
<td>14</td>
</tr>
</tbody>
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* The relapse rate was calculated as follows: (cure rate at 2 weeks − cure rate at 6 weeks)/cure rate at 2 weeks × 100.
