Randomized Comparative Study of Amoxicillin-Clavulanic Acid and Co-trimoxazole in the Treatment of Acute Urinary Tract Infections in Adults

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The efficacy and safety of amoxicillin-clavulanic acid were compared with those of co-trimoxazole in the treatment of acute urinary tract infections. A total of 104 patients (mean age, 52 years) with clinical and laboratory evidence of acute urinary tract infection were enrolled in the study. Characteristics and infecting organisms were equivalent in both groups of patients. Escherichia coli was the predominant bacteria pathogen in both groups. Both drugs resulted in clinical improvement in 100% of the patients; bacteriological cure after the termination of therapy was 95% with amoxicillin-clavulanic acid and 83% with co-trimoxazole ($P < 0.001$).

Side effects were not severe enough to necessitate discontinuation of the antimicrobial agents. Amoxicillin-clavulanic acid is effective and safe therapy for acute urinary tract infections caused by susceptible bacteria.

The formulation of amoxicillin with clavulanic acid (potassium salt) possesses activity against many bacteria which produce plasmid-mediated β-lactamases (1–3, 5). Clavulanic acid is a naturally occurring β-lactam product of Streptomyces clavuligerus and is a potent inhibitor of bacteria β-lactamases, although it has little essential antibacterial activity (7). The formulation of amoxicillin and clavulanic acid has synergistic antibacterial activity against amoxicillin-resistant strains capable mainly of producing penicillinase (1–3, 5).

In this prospective randomized study of adult patients with acute urinary tract infections, the efficacy of this new antimicrobial combination was compared with that of co-trimoxazole, an agent with proven usefulness in this clinical setting (6).

Adult patients admitted to the hospital with acute urinary tract infections were enrolled in the study after informed consent was obtained. Each patient considered for inclusion carried a clinical diagnosis of acute urinary tract infection. All patients initially presented with symptoms referable to acute urinary tract infections, including dysuria, urinary frequency, flank pain, costovertebral angle tenderness, chills, and high fever ($>38^\circ$C). Initially, 60 patients had temperatures $>38^\circ$C (31 in the amoxicillin-clavulanate group and 29 in the co-trimoxazole group).

The major criterion for inclusion was the presence of $>10^5$ CFU of the same bacterium per ml in each of three consecutive clean-catch midstream urine specimens and pyuria (at least 5 to 10 leukocytes per high-power field).

Criteria for exclusion. Criteria for exclusion were (i) abnormal renal function (serum creatinine $>2.0$ mg/100 ml), (ii) known allergy to the penicillins or sulfonamides, (iii) pregnancy, (iv) concomitant infection, (v) in-dwelling Foley catheters, (vi) renal calculi or complete urinary tract obstruction, and (vii) rapidly progressing fatal illness.

Patients admitted to the study were randomized to receive either amoxicillin-clavulanic acid in a fixed combination or co-trimoxazole. All the patients were examined daily, and all clinical data were recorded in standardized form. The following parameters were obtained before therapy: hematocrit, hemoglobin, leukocyte count, platelet count, serum creatinine, blood urea nitrogen, serum glutamic oxalacetic and pyruvic transaminases, bilirubin, alkaline phosphatase, blood sugar, urinalysis, and clean-catch midstream or catheterization urine for quantitative culture and testing of susceptibility to antimicrobial agents. The laboratory profile and urine culture were repeated 2 to 3 days after the start of therapy, at the end of therapy, and 10 days and 6 weeks later.

Antibiotic dose and administration. Amoxicillin-clavulanic acid was given per os in a dose of one tablet per 8 h for 10 days. Each tablet contained 250 mg of amoxicillin and 125 mg of clavulanic acid in a fixed combination. Co-trimoxazole was administered by the same route every 12 h. Each tablet contained 160 mg of trimethoprim and 800 mg of sulfamethoxazole.

The therapeutic effects of both agents were assessed on the basis of the sequential urine cultures obtained from each patient. The criteria were as follows. Cure was defined as clinical improvement and eradication of the bacteria at the time the drug was discontinued and on follow-up. Recurrent infections were considered to represent a relapse if the organism isolated after therapy was of the same species. Reinfection was defined as the initial eradication of the responsible organism followed by a new infection with one or more different organisms after the treatment was discontinued. Superinfection was defined as the appearance of one or more new organisms during treatment. Persistence of an organism and relapse were considered as failure. Results were compared by using the chi-square test for discreet variables and Student’s $t$ test for continuous variables. A $P$ value of less than 0.05 was considered significant.

A total of 112 patients were initially enrolled in the study. Eight patients were excluded after 48 h of treatment due to sterile or contaminated admission urine cultures. Contamination, defined as foreign organisms developing accidentally in a pure culture, was observed in four specimens. The remaining 104 patients met all the clinical and microbiological criteria for the diagnosis of acute urinary tract infection. The age of the patients ranged from 18 to 73 years, with a mean of 52 years. There were 43 males (23 and 20 in the amoxicillin-clavulanic acid and co-trimoxazole group, respectively) and 61 females (31 and 30 in the amoxicillin-clavulanic acid and co-trimoxazole group, respectively). A
TABLE 1. Original infecting organisms and results at the end of therapy in 104 patients treated with amoxicillin-clavulanic acid and co-trimoxazole

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Amoxicillin-clavulanic acid</th>
<th>Co-trimoxazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Success</td>
<td>Failure</td>
</tr>
<tr>
<td>E. coli</td>
<td>45</td>
<td>1</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>S. faecalis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Total of 31 patients in the amoxicillin-clavulanic acid group and 30 in the co-trimoxazole group had temperatures under 38°C. There were no significant differences between the two groups in age, sex, admission temperature, and laboratory parameters.

The most common isolated pathogen in both groups was *Escherichia coli*: 46 in the amoxicillin-clavulanic acid-treated patients and 42 in the co-trimoxazole-treated patients. *Klebsiella pneumoniae* was the causative organism in four patients treated with amoxicillin-clavulanic acid and in three patients treated with co-trimoxazole. *Proteus mirabilis* was the causative organism in two and three patients treated with amoxicillin-clavulanic acid and co-trimoxazole, respectively. *Streptococcus faecalis* and *Staphylococcus aureus* were the pathogenic organisms in one patient of each group (Table 1).

Clinical responses were equivalent for the two treatments. Resolution of fever to less than 37.5°C took an average of 2.4 days (range, 1 to 4 days) with amoxicillin-clavulanic acid and 2.8 days (range, 1 to 5 days) with the co-trimoxazole therapy. All symptoms of urinary tract infection disappeared in all patients in both treatment groups. Clinical results generally correlated with bacteriuria.

The bacterial pathogen was eliminated from all 54 patients in the amoxicillin-clavulanic acid-treated group after the first 2 days of therapy. Six patients receiving co-trimoxazole had positive cultures after 2 days of treatment: two patients with *E. coli*, three with *K. pneumoniae*, and one with *P. mirabilis*.

At the termination of therapy, urine cultures were sterile for 51 (95%) of 54 patients treated with amoxicillin-clavulanic acid and 41 (85%) of 50 patients treated with co-trimoxazole. This difference was statistically significant ($P < 0.001$).

However, 5 patients of the 54 treated with amoxicillin-clavulanic acid developed a recurrence of bacteriuria within 6 weeks after therapy; two of these recurrences were due to relapse, and three were due to reinfection. Nine patients treated with co-trimoxazole also developed bacteriuria during the 6 weeks after therapy: four of these recurrences were due to relapse, and five were due to reinfection. The difference in the recurrence rates between the two groups was statistically significant. No relapse was associated with a resistant organism. Side effects attributable to the antimicrobial agents were minor in both groups of patients. Evidence of drug toxicity occurred in 10 (22.2%) patients treated with amoxicillin-clavulanic acid and 12 (24%) patients treated with co-trimoxazole, but the difference was not statistically significant. The most common reported side effects were as follows. Four of the patients treated with amoxicillin-clavulanic acid developed hypersensitivity reactions (two maculopapular rashes and two eosinophilia). Three patients developed mild diarrhea, one had vomiting, and two had vaginitis. Among patients treated with co-trimoxazole, four developed diarrhea, two had rashes, three had nausea, and two had constipation. Renal function did not change during either mode of therapy. No hepatic or hematological reaction developed in either group of patients. In none of the patients did development of side effects necessitate discontinuation of the therapy.

In this randomized study, we compared amoxicillin-clavulanic acid with co-trimoxazole for the treatment of acute urinary tract infections in adult patients. We attempted to exclude patients with uncomplicated cystitis and acute urethral syndrome.

This study showed that amoxicillin-clavulanic acid is more effective than co-trimoxazole for eradicating susceptible pathogens from the urine of patients with acute urinary infections. The primary cure rate was 95% in the amoxicillin-clavulanic acid group, compared with 83% in the co-trimoxazole group. Moreover, on follow-up the cumulative bacteriological cure rate in the amoxicillin-clavulanic acid group was greater than in the co-trimoxazole group.

Davies et al. (2) compared the efficacy of amoxicillin-clavulanic acid with that of co-trimoxazole in 347 patients with various infections, including acute infections of the urinary tract. Of those patients in whom bacteria were isolated, the proportion that had a good clinical response was greater among patients treated with amoxicillin-clavulanic acid than among patients treated with co-trimoxazole.

No serious side effects were observed in the two groups of patients, and tolerance was generally good. A few patients developed hypersensitivity reactions, and it is of interest to note that vaginitis developed in two patients treated with amoxicillin-clavulanic acid. The high incidence of nausea in the co-trimoxazole group was surprising, because it was contrary to the experience of most authors (4, 8).

On the basis of the results of this randomized study comparison, we considered amoxicillin-clavulanic acid to be more effective than co-trimoxazole in the treatment of patients with acute urinary tract infections caused by susceptible bacteria.

LITERATURE CITED