Amoxicillin-Clavulanic Acid Versus Cefaclor in the Treatment of Urinary Tract Infections and Their Effects on the Urogenital and Rectal Flora

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In a double-blind randomized study, amoxicillin-clavulanic acid (AM-CL) was compared with cefaclor for the treatment of acute urinary tract infections in 107 college women. A total of 53 patients received amoxicillin (250 mg) and clavulanic acid as the potassium salt (125 mg), and 54 received cefaclor (250 mg); each drug was administered every 8 h for 10 days. The cure rates at 1 and 4 weeks after treatment were 96 and 78%, respectively, in the AM-CL group and 92 and 75%, respectively, in the cefaclor group (P > 0.10). After AM-CL treatment, the prevalence of amoxicillin-resistant Escherichia coli significantly increased in the rectal flora. Also, the frequency of bacterial resistance to amoxicillin, AM-CL, and cefaclor increased among the urinary pathogens causing subsequent urinary tract infections (P < 0.05). There were no adverse reactions in the cefaclor group; however, six patients in the AM-CL group (12%) experienced diarrhea, nausea, or vomiting (P < 0.05). Elevated transaminase enzyme levels were observed in 23% of the patients in the AM-CL group and in 6% of the patients in the cefaclor group (P < 0.05). Symptomatic Candida vaginitis developed in 16 and 13% of the patients in the AM-CL and cefaclor groups, respectively (P > 0.10).

Bacterial resistance to the β-lactam antibiotics is largely due to the production of a β-lactamase (1, 5, 20). Clavulanic acid inhibits many of these enzymes (16). A combination of amoxicillin (AM) and clavulanic acid (CL) is effective against a variety of β-lactamase-positive bacteria (2, 4, 10, 12, 15). The purposes of this study were (i) to compare the efficacy and safety of AM-CL with the efficacy and safety of cefaclor in the treatment of acute urinary tract infections (UTIs) in young women, (ii) to relate therapeutic responses to the results of the antibody-coated bacteria test (ACBT), and (iii) to assess the emergence of resistant members of the Enterobacteriaceae in the rectal and urogenital areas after treatment.

MATERIALS AND METHODS

Patient criteria. The study group consisted of college women who came to the Kidney Clinic of the University of Florida Student Health Services with symptoms of acute UTIs. The criteria for inclusion were as follows: (i) symptoms such as dysuria, urgency, and suprapubic or flank pain; (ii) at least one bacterium in each random high-power microscopic field of an unstained and uncentrifuged urine specimen; and (iii) ≥10^5 CFU of a bacterium per ml in each of three consecutive urine specimens. Initially, 111 patients entered the study, but 4 had negative urine cultures and did not qualify, leaving 107 patients in the study. Excluded from the study were pregnant or lactating women and women with impaired renal or liver function, radiographically proven obstructive uropathy, or a history of allergy to penicillins or cephalosporins. Patients who had received antimicrobial agents during the preceding week were also excluded.

Collection, processing, and analysis of specimens. A specially trained nurse instructed each patient to submit three clean-catch midstream urine specimens within 24 h before treatment. Each urine specimen was analyzed and cultured. Specimens were collected from the vagina, periurethral area, and rectum with Culturette rayon-tipped swabs (Scientific Products Div., Evanston, Ill.) for culture and susceptibility testing before treatment and 1 week after treatment ended. These specimens were also obtained before treatment of recurrent UTIs.

Bacteriologic techniques. Isolation and quantitative bacterial counts were performed with a calibrated platinum loop which delivered 0.01 ml of urine onto blood agar and MacConkey plates. Gram-negative organisms were identified by using the API-20E system (Analytab Products, Plainview, N.Y.) (8, 19). Staphylococcus saprophyticus was identified by a previously described method (13). Antibiotic susceptibility was tested by the disk diffusion method using 30-μg disks of AM-CL (20 μg of AM and 10 μg of the potassium salt of CL), 10-μg disks of ampicillin (for AM), and 30-μg disks of cefaclor (3). Bacterial isolates were considered susceptible to ampicillin and cefaclor when the disk zone sizes were ≥14 and ≥15 mm, respectively. Members of the Enterobacteriaceae and gram-positive cocci were considered susceptible to AM-CL when disk zone sizes were ≥17 and ≥24 mm, respectively.

The swabs from vaginal, periurethral, and rectal areas were streaked onto MacConkey and blood agar plates. Each colony type was identified, and susceptibility was tested as described above. Vaginal specimens were also tested for the presence of Candida albicans by using potassium hydroxide smears and culture on Nickerson agar (GIBCO Diagnostics, Lawrence, Mass.).

Escherichia coli isolates identified to serotype were obtained from the Centers for Disease Control, Atlanta, Ga. Antisera to various Escherichia coli O antigens were produced by the method described by Ewing (9). Each working antiserum solution contained 19.8 ml of sterile saline, 2

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susceptibilities are shown in Table 2. Of the 77 E. coli urinary pathogen isolates, 69 were serotyped. The common serotypes were 018 (19%), 06 (17%), 01 (10%), and 075 (6%). A total of 38% of the E. coli isolates were not typeable to the serogroups used. Of the urinary pathogens tested, 95% were susceptible to AM-CL, 95% were susceptible to cefaclor, and 78% were susceptible to AM.

Clinical and bacteriologic responses to treatment. The mean duration for disappearance of symptoms after initiation of treatment was 27 h (range, 3 to 82 h) in the AM-CL group and 26 h (range, 2 to 116 h) in the cefaclor group. A total of 51 of 53 patients in the AM-CL group and 53 of 54 patients in the cefaclor group completed treatment. Urine cultures were sterile on day 2 of treatment and 2 days after treatment ended in these patients. At 1 and 4 weeks after treatment ended, the AM-CL group had cure rates of 96 and 78%, respectively, and in the cefaclor group the cure rates were 92 and 75%, respectively (Table 3). There were 15 recurrences in the AM-CL group and 20 recurrences in the cefaclor group by 12 weeks after treatment ended. As determined by the life table method (6), the cumulative recurrence rates by 12 weeks after treatment ended were 33% in the AM-CL group and 39% in the cefaclor group (Fig. 1). The overall therapeutic results did not differ significantly in the two groups.

One patient in the AM-CL group had an AM-CL-resistant Enterobacter aerogenes in vitro, but she achieved long-term cure. Four patients in the cefaclor group, two infected with a cefaclor-resistant Escherichia coli strain and two infected with a cefaclor-resistant Enterobacter cloacae strain, responded well to treatment. Three of the four had long-term cure, and one had a reinfection 24 days after treatment was completed.

Test of localization. Of the 53 patients in the AM-CL group, 9 were ACBT positive, and 44 were ACBT negative. Of the 54 patients in the cefaclor group, 9 were ACBT positive, 43 were ACBT negative, and 2 had nonspecific test results. The clinical characteristics of the patients were similarly distributed in the ACBT-positive and -negative groups. All patients in both groups with positive ACBT maintained a long-term cure, whereas the long-term cure rate was 78% in the ACBT-negative AM-CL group and 75% in the ACBT-negative cefaclor group (P > 0.10).

Bacterial resistance and colonization in the urogenital and rectal areas. Specimens were obtained from periurethral, vaginal, and rectal areas of 49 patients in the AM-CL group and 49 patients in the cefaclor group. Table 4 shows the distribution of bacterial isolates according to culture area before treatment and 1 week after the end of treatment. After AM-CL treatment, the prevalence of Escherichia coli isolates resistant to AM increased 20% in the rectal area (P < 0.05) and did not significantly change in the periurethral and vaginal areas. The prevalence of other members of the Enterobacteriaceae resistant to AM did not significantly change in the periurethral, vaginal, and rectal areas. No significant change occurred in the prevalence of Escherichia coli and other members of the Enterobacteriaceae resistant to AM-CL or cefaclor in these areas. After treatment with cefaclor, no significant change occurred in the susceptibility pattern of Escherichia coli and other members of the Enterobacteriaceae colonizing urogenital and rectal areas.

Emergence of resistant urinary pathogens. In patients in the AM-CL group with recurrent UTIs which occurred within 12 weeks after treatment ended, the prevalence of AM-resistant urinary pathogens increased 30%, the prevalence of AM-CL-resistant urinary pathogens increased 18%, and the prevalence of cefaclor-resistant urinary pathogens increased 18% (P < 0.05) compared with the pathogens causing the initial infections. In patients in the cefaclor group with recurrent UTIs, the prevalence of resistant urinary pathogens did not significantly change compared with the pathogens causing the initial infections (Table 5).

Side effects. There were no adverse reactions in the cefaclor group. Six patients (12%) in the AM-CL group experienced adverse drug reactions (P < 0.05). Five had transient diarrhea without interruption of therapy, and one developed mild nausea and vomiting on the last day of therapy.

A total of 50 patients in the AM-CL group and 52 patients in the cefaclor group were screened for vaginal candidiasis before treatment and 1 week after the end of treatment. The prevalence of vaginal candidiasis in the initial patient screening was shown in Table 1. After treatment, Candida vaginitis, with vaginal discharge or vulvar irritation or both, developed in eight patients (16%) in the AM-CL group and in seven

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### TABLE 3. Distribution of patients by treatment group and bacteriologic response through 4 weeks after treatment ended

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. who completed treatment</th>
<th>Short-term cure</th>
<th>Failure</th>
<th>Relapse</th>
<th>Reinfection</th>
<th>Long-term cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM-CL</td>
<td>51</td>
<td>49 (96)*</td>
<td>0</td>
<td>4 (8)</td>
<td>7 (14)</td>
<td>40 (78)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>53</td>
<td>49 (92)</td>
<td>0</td>
<td>11 (21)</td>
<td>2 (4)</td>
<td>40 (75)</td>
</tr>
</tbody>
</table>

* The numbers in parentheses are percentages.
TABLE 4. Distribution of bacterial isolates according to culture area before treatment and 1 week after treatment endeda

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients</th>
<th>Area of culture</th>
<th>Relation to treatment</th>
<th>No. with positive cultures</th>
<th>Escherichia coli</th>
<th>Other members of the Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of isolates</td>
<td>No. resistant to:</td>
<td>No. of isolates</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AM</td>
<td>AM-CL</td>
<td>Cefaclor</td>
</tr>
<tr>
<td>AM-CL</td>
<td>49</td>
<td>Periurethral</td>
<td>Before</td>
<td>37</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>33</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal</td>
<td>Before</td>
<td>32</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>24</td>
<td>19</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td>Rectal</td>
<td>Before</td>
<td>49</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>45</td>
<td>48</td>
<td>16a</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>49</td>
<td>Periurethral</td>
<td>Before</td>
<td>38</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>32</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal</td>
<td>Before</td>
<td>35</td>
<td>34</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>30</td>
<td>26</td>
<td>7</td>
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<td></td>
<td></td>
<td>Rectal</td>
<td>Before</td>
<td>49</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>After</td>
<td>47</td>
<td>55</td>
<td>11</td>
</tr>
</tbody>
</table>

a Ampicillin disks were used to test susceptibility to AM.

patients (13%) in the cefaclor group (P > 0.10). Twelve additional patients (24%) in the AM-CL group and five patients (10%) in the cefaclor group became asymptomatic carriers of vaginal candidiasis (P > 0.10).

Blood chemistry and hemograms. After completion of treatment, elevated transaminase enzyme levels were found in 12 patients (23%) in the AM-CL group and in 3 patients (6%) in the cefaclor group (P < 0.05). In the AM-CL group, 8 of the 12 patients had elevated serum glutamic oxalacetic transaminase levels (44 to 117; normal is 0 to 40 IU/liter), and four had elevated serum glutamic pyruvic transaminase levels (43 to 81; normal is 0 to 40 IU/liter). In the cefaclor group, two of the three patients had serum glutamic oxalacetic transaminase levels of 43 to 62, and one patient had a serum glutamic pyruvic transaminase level of 46. In the AM-CL group, 6 other patients (12%) had eosinophilia (absolute count, ≥500/mm³), and one patient (2%) had neutropenia (absolute polymorphonuclear count, ≤1,500/mm³). All abnormal laboratory findings were transient and returned to normal within 2 weeks after treatment ended.

DISCUSSION

AM-CL and cefaclor both had a broader in vitro antibacterial activity than AM alone; 5% of urinary pathogens were resistant in vitro to AM-CL in this study. Bacterial resistance to AM-CL is occasionally reported, which may be explained by the inactivity of CL against some varieties of β-lactamases (4, 16, 20). Both AM-CL and cefaclor were efficacious in eliminating urinary pathogens regardless of the in vitro resistance of the organisms. The therapeutic results were in agreement with previous results (2, 4, 10, 12, 14, 15).

Compared with cefaclor treatment, treatment with AM-CL was associated with an increase in the prevalence of *Escherichia coli* isolates resistant to AM in the rectal flora, and an increase in the prevalence of resistance among urinary pathogens of subsequent UTIs to AM, AM-CL, and cefaclor. However, these results may not be conclusive, since quantitative culture tests were not done in this study. Emergence of resistant bacterial strains has been reported with the use of broad-spectrum β-lactam antibiotics (18). The exact mechanism of this phenomenon and the development of cross-resistance to other antibiotics is not fully understood.

The response to therapy based on the ACBT was paradoxical. Patients with positive ACBTS had a higher cure rate at 1 and 4 weeks after treatment ended than patients with negative ACBTS in both treatment groups. If patients with positive ACBTS had renal involvement, one would expect them to respond less favorably to treatment than patients with negative ACBTS. However, the positive ACBT group was small (18 patients), and in our opinion these results are not conclusive. In previous studies we have found no correlation between response to treatment and ACBT results (11, 12; A. Iravani and G. A. Richard, Pediatr. Res. 15:443, 1981).

By 12 weeks after therapy ended, a recurrent infection had developed in 33 and 39% of the patients in the AM-CL and cefaclor groups, respectively. In our experience, regardless of the antibiotic used in treatment, about one-third of women with acute UTIs develop recurrent infections by 3 months after treatment ends (11).

Cefaclor was tolerated well by all the patients, and the adverse reactions occurring with AM-CL (12%) were comparable to the reactions described in previous reports (4, 12, 14). The frequency of elevated transaminase levels (serum

TABLE 5. Emergence of resistant urinary pathogens in patients with recurrences occurring after treatment ended within 12 weeks

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Initial infections</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of bacterial isolates</td>
<td>No. resistant to:</td>
</tr>
<tr>
<td></td>
<td>AM</td>
<td>AM-CL</td>
</tr>
<tr>
<td>AM-CL</td>
<td>53</td>
<td>9 (17)a</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>54</td>
<td>15 (20)</td>
</tr>
</tbody>
</table>

a The numbers in parentheses are percentages.
glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase) was significantly higher in the AM-CL group (23%) than in the cefaclor group (6%) and was higher than our previous report of 4% in patients treated with AM-CL (12). These observations warrant further safety evaluation of AM-CL.

The incidence of symptomatic vaginal candidiasis was relatively high following both AM-CL (16%) and cefaclor (13%) treatment. In a previous trial we found an incidence of symptomatic vaginal candidiasis of 14% following the use of AM-CL (12).

Both AM-CL and cefaclor appeared to be equally efficacious in the treatment of UTIs in college women. However, there was a high incidence of vaginal candidiasis following the use of both drugs. Elevated transaminase enzyme levels and emergence of resistant bacteria were associated with AM-CL treatment. Further investigations are warranted in order to better understand the extent and mechanisms of these findings.

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LITERATURE CITED