Double-Blind Comparative Study of Two Dosage Regimens of Cefaclor and Amoxicillin-Clavulanic Acid in the Outpatient Treatment of Soft Tissue Infections

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A total of 88 patients were enrolled in a double-blind comparison of cefaclor and amoxicillin-clavulanic acid for the outpatient treatment of soft tissue infections (abscesses, cellulitis, and impetigo). In 84 clinically evaluable patients, high cure rates were obtained for all treatment groups (64 to 85%). Patients who received amoxicillin-clavulanic acid had a much higher incidence of gastrointestinal side effects than did patients who received cefaclor (34 versus 3%, \( P < 0.005 \)). However, only five patients with gastrointestinal reactions to amoxicillin-clavulanic acid had symptoms severe enough to warrant halting the completion of antibiotic therapy.

Clavulanic acid is a potent inhibitor of staphylococcal beta-lactamases, as well as some beta-lactamases of gram-negative aerobic and anaerobic bacteria (18). Clavulanic acid has been recently combined with amoxicillin in two different dosage preparations (Augmentin; Beecham Laboratories). Both formulations of Augmentin provide a sufficient dosage of clavulanic acid (125 mg) to expand the in vivo and in vitro antibiotic activity of amoxicillin (5). I report the results of a clinical double-blind trial of 88 outpatients who were randomized to receive either cefaclor (CEF), a broad-spectrum oral cephalosporin, or amoxicillin-clavulanic acid (A+C).

MATERIALS AND METHODS

Over a 1-year period, 88 patients consented to participate in a comparative double-blind study. All participants were adults with no known history of penicillin allergy. Of these 88 patients, 60 with fever or extensive soft tissue infections were given high-dose antibiotic pills (cefaclor [500 mg] or amoxicillin trihydrate [500 mg] plus potassium clavulanate [125 mg]) three times per day; 28 with minor abscesses were given low-dose antibiotic pills (cefaclor [250 mg] or amoxicillin trihydrate [250 mg] plus potassium clavulanate [125 mg]) three times per day. Patients were given unmarked, consecutively numbered antibiotic vials prepared by Beecham Laboratories by using a table of random numbers. Patients made at least three outpatient visits (at the initiation, middle, and completion of therapy) to monitor the clinical course and adverse side effects. Complete blood counts, urinalyses, and sequential multiple analyzer (SMA-12) measurements were performed at the beginning and end of antibiotic therapy. Wound cultures were obtained from draining pus or after incision and drainage. Terminal wound cultures were done 1 to 3 days after completion of therapy, unless the skin infection was completely healed. Cultures were obtained with cotton swabs (Culturettes; Marion Laboratories) and inoculated on 5% sheep blood and MacConkey agar and in thioglycolate broth. The agar plates were incubated in 5% \( \text{CO}_2 \) at 35°C for 48 h, and the thioglycolate tubes were incubated at 35°C for 7 days. Antibiotic treatment was continued for a minimum of 5 days and for 2 to 3 days beyond the time when the infection was cured (maximum, 10 days), except that all streptococcal infections were treated for 10 days. A patient was considered clinically cured if the skin infection was healed at the time the drug was discontinued. If the skin infection had subsided to less than half of its initial size, the patient was considered clinically improved. Statistical differences between treatment groups were analyzed by the chi-square test. Antibiotic susceptibility testing was performed by the agar overlay diffusion method (3), using antibiotic disks containing cephalothin (30 mg), oxacillin (1 mg), ampicillin (10 mg), or amoxicillin (20 mg) plus clavulanic acid (10 mg). For gram-positive cocci tested against A+C, a zone size of \( \geq 20 \text{ mm} \) was considered to indicate susceptibility, and a zone size of \( <19 \text{ mm} \) was considered to indicate resistance. For gram-negative bacteria, an A+C zone size of \( \leq 13 \text{ mm} \) was considered to indicate susceptibility, a zone size of 14 to 17 mm was considered to indicate an intermediate reaction, and a zone size of \( \geq 18 \text{ mm} \) was considered to indicate susceptibility (7). Ampicillin, oxacillin, and cephalothin susceptibilities were interpreted by standards set by the National Committee for Clinical Laboratory Standards for disk susceptibility testing (11).

RESULTS

Clinical characteristics of the study population. Of the 88 treated patients, 4 were considered...
TABLE 1. Responses to each antibiotic treatment regimen

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>No. of patients</th>
<th>% Cured</th>
<th>% Improved</th>
<th>% Eradication of bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+C (high dose)</td>
<td>28</td>
<td>68</td>
<td>32</td>
<td>75</td>
</tr>
<tr>
<td>CEF (high dose)</td>
<td>30</td>
<td>67</td>
<td>33</td>
<td>63</td>
</tr>
<tr>
<td>A+C (low dose)</td>
<td>13</td>
<td>85</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>CEF (low dose)</td>
<td>13</td>
<td>69</td>
<td>31</td>
<td>70</td>
</tr>
</tbody>
</table>

therapeutically nonevaluable because of inadequate clinical information or follow-up. The mean age of the patients receiving CEF was 37.9 years (range, 15 to 73 years), with 65.9% male predominance. The mean age of the patients receiving A+C was 37.5 years (range, 15 to 77 years), with the same sex incidence as the CEF group. Only about 15% of the study patients had predisposing illnesses such as diabetes mellitus or an underlying dermatological condition.

The most common type of skin infections in the 64 cases were abscesses, of which 63% involved an extremity, 23% involved the trunk, 11% involved the face, and 3% involved the perirectal area. The remaining patients had cellulitis, surgical wound infections, impetigo, or lymphadenitis.

Bacteriological isolates. Of the 88 isolates, 29 were Staphylococcus aureus, 18 were group A Streptococcus, 18 were skin organisms (S. epidermidis, Corynebacterium sp., and Propionibacterium sp.), 12 were gram-negative aerobic bacteria, 8 were anaerobic bacteria, and 3 were Enterococcus sp. No bacteria were isolated from 9 patients at the time of initial culturing. With the exception of three Pseudomonas isolates, most bacteria were susceptible to both CEF and A+C. Only 24% of S. aureus isolates were susceptible to ampicillin, but 100% were susceptible to cephalothin. For A+C, 59% of S. aureus isolates were considered susceptible in vitro (≥20 mm zone size), 37% produced moderately large zones of inhibition (15 to 19 mm), and 4% produced small zones of inhibition (<15 mm). No S. aureus isolates were resistant to oxacillin.

Clinical and bacteriological responses. Table 1 shows the clinical and bacteriological responses to each antibiotic therapy. All study patients showed at least 50% clinical improvement, with 67 to 85% cure rates. There were no significant differences in the clinical response rate among the different treatment groups. In both low- and high-dose regimens, A+C produced higher rates of bacterial eradication. Among S. aureus infections, both susceptible and moderately susceptible isolates responded equally to A+C. In two cases, S. aureus isolates with zones of in vitro inhibition of <15 mm to A+C were not eradicated with A+C therapy.

Adverse effects. There was a significant difference in gastrointestinal side effects (P < 0.005) in the patients who received A+C versus CEF. Table 2 shows a comparison of all 88 patients who received antibiotics. With high-dose regimens, 26.7% of the A+C patients developed loose stools or diarrhea, and 19.7% developed nausea or vomiting, as compared with only a 3.3% incidence of gastrointestinal side effects in the CEF patients. In the low-dose groups, 14.3% of the A+C patients developed diarrhea, and 28.5% had nausea, as compared with only a 3.5% incidence of gastrointestinal symptoms in the CEF patients. However, only 5 of the 44 patients who received A+C had symptoms severe enough to warrant discontinuing antibiotic treatment, but treatment had to be discontinued for 1 of the 44 patients who received CEF. All adverse side effects abated at the cessation of antibiotic therapy. No significant laboratory abnormalities occurred with A+C. One patient who received CEF developed an asymptomatic eosinophilia of 14% not associated with rash. Despite my requests, this patient refused subsequent follow-up treatment for his eosinophilia.

DISCUSSION

This clinical trial confirms limited reports on the efficacy of A+C for the treatment of soft tissue infections (2, 10). When compared in a double-blind fashion, A+C was as clinically efficacious as CEF for the treatment of outpatient cutaneous abscesses predominately caused by gram-positive bacteria. A+C produced high-

TABLE 2. Adverse side effects of each treatment regimen

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>No. of patients tested</th>
<th>No. of patients with side effects</th>
<th>No. of patients discontinuing antibiotic</th>
<th>Diarrhea or loose stools</th>
<th>Nausea or vomiting</th>
<th>Rash or urticaria</th>
<th>Vaginal candidiasis</th>
<th>Malaise</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+C (high dose)</td>
<td>30</td>
<td>12</td>
<td>3</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CEF (high dose)</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>A+C (low dose)</td>
<td>14</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CEF (low dose)</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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er rates of bacterial eradication than did CEF. This higher rate of eradication has been found to be statistically significant ($P < 0.01$) in combined data collected by Beecham Laboratories (E. Aten, M. D. Reese, and H. C. Neu, submitted for publication). Although there was no significant difference in either the clinical or the bacteriological response to each antibiotic, *S. aureus* was less frequently susceptible to A+C than was cephalosporin. This finding is somewhat in disagreement with some previous findings. Van Landuyt et al. reported that A+C inhibited 93% of beta-lactamase-producing *S. aureus* isolates at a concentration of 2 mg/ml (16). By disk diffusion testing with the 30-μg A+C disk, Perryman et al. (13) found that 88% of *S. aureus* isolates were susceptible to A+C, and Abbas et al. (1) reported that 94.6% of *S. aureus* isolates from wounds were susceptible. However, these authors did not state the zone size range for the susceptible category. Most of the resistant *Staphylococcus* isolates in this study produced a moderate zone size of 15 to 19 mm, indicating minimal inhibitory concentrations of 4 to 25 mg/ml (E. Aten, Beecham Laboratories, personal communication). These moderately resistant *S. aureus* isolates clinically responded to A+C in a fashion similar to that of sensitive *S. aureus* isolates.

The main difference between antibiotic treatment groups in this study was the incidence of adverse effects. Over 40% of patients who received A+C had side effects regardless of dosage, whereas only 7% of the CEF-treated patients suffered any untoward effects ($P < 0.005$). This low rate of CEF side effects was similar to rates given in previously published CEF studies (6, 8). Amoxicillin alone has been reported to have an adverse side effect rate of 5 to 6% (12). Double-blind studies comparing CEF and amoxicillin in adults have shown a similar incidence of adverse effects (4, 9). The high rate of gastrointestinal reactions in this study (34% of all A+C-treated patients) agrees with the results of Watson and Mahendra, who reported that 156 of 482 patients treated with A+C had side effects (32% of patients), including 15% with diarrhea, 6% with nausea or vomiting, and 2% with rash (17). Stamboulian et al. found that the addition of clavulanic acid to amoxicillin caused more nausea than did amoxicillin alone (14). Staniforth et al. demonstrated that nausea may be reduced by taking A+C with food, without affecting bioavailability (15).

In this trial, most side effects were mild and well tolerated. Only 5 of 18 A+C patients discontinued their medication because of intolerance, as compared with 1 of 3 CEF patients. Both antibiotics were very efficacious for the treatment of outpatient skin and soft tissue infections. Therefore, the choice between these antibiotics may be dependent upon drug cost and other differences not measured in this comparative study.

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**LITERATURE CITED**
