Comparative Efficacy of Cefotiam Versus Cephalothin in the Therapy of Skin and Soft Tissue Infections

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Cefotiam was evaluated by a comparative open-label randomized trial with cephalothin in the therapy of skin and soft tissue infections in 39 patients. The most common organism isolated was Staphylococcus aureus (78%). We established evidence of primary infection with gram-negative bacilli in four patients, three of whom were diabetic. Eight patients had mixed infections or superinfections. No patient was evaluated as a treatment failure; for 10 of 39 patients we were unable to recover an etiological agent but demonstrated a clinical cure. Cefotiam was found to be as effective as cephalothin in the therapy of skin and soft tissue infections.

Cefotiam, a new cephalosporin derivative, has been shown to possess a broad spectrum of in vitro activity against the common gram-positive bacteria as well as aerobic gram-negative bacilli such as Klebsiella, Proteus, Enterobacter, and Citrobacter species (8, 11, 12). Because of the possibility of primary infection of the skin and soft tissues with microorganisms resistant to penicillinase-resistant penicillins (2–4, 6, 7, 13), we elected to treat patients in an open-label randomized trial with either cefotiam or cephalothin. We actively searched for patients with gram-negative skin and soft tissue infections.

We report on the clinical efficacy of cefotiam in this patient population as compared with cephalothin. In addition, a comparative in vitro susceptibility assay of the organisms responsible for these infections was performed with both cefotiam and cephalothin.

Patients admitted to the medical or surgical services of the Edward Hines Jr. Veterans Administration Hospital (Hines, Ill.) were asked to participate over a 14-month study period from January 1982 through March 1983. Minimal requirements for entry into the study included clinical evidence of skin and soft tissue infections of bacterial origin, i.e., local erythema, tenderness, swelling, and increased warmth.

The majority of patients (38 of 39) had cellulitis; 1 had impetigo. In keeping with Food and Drug Administration regulations, no persons were under 18 years old, allergic to cephalosporins, or receiving other antibiotics. Additional exclusion criteria included prior antibiotic therapy within the 48 h preceding entry into the study, allergy to local anesthetics of the amide type, impaired immunological function, and underlying gangrenous or necrotic lesion at the site of infection. All were males. Ages ranged from 23 to 84 with a mean age of 52 years among patients in the cephalothin arm of the study and 59.7 years among those patients in the cefotiam arm of the study; this was not statistically significant.

After obtaining written informed consent, patients were started on either cefotiam or cephalothin according to a randomization schedule known only to the dispensing pharmacy. Of the 39 patients, 22 were randomized to cefotiam. Nine patients were febrile (>38.4°C).

Specimens were obtained by needle aspiration of abscesses, pustules, vesicles, and bullae after the skin was cleansed with povidone-iodine (iodophor-pvp, Cliniswab; Clinipad Corp., Guilford, Conn.). When no such lesion was noted, sterile non-bacteriostatic saline was injected subcutaneously at the leading edge of the area of cellulitis, and the aspirate was sent for culture and sensitivity. No swab cultures of open surface lesions were obtained for diagnostic culture in this study. Upon receipt in the clinical microbiology laboratory of the hospital, all specimens were plated onto sheep blood agar and MacConkey agar and were inoculated into thioglycolate broth. No anaerobic cultures were performed.

After incubation at 37°C for 18 to 24 h, plates were examined for isolation and identification of potential pathogens. All isolates were then tested by serial twofold dilution for the MICs of cefotiam and cephalothin at an inoculum of 106 CFU/ml in unsupplemented Mueller-Hinton broth (1). Blood cultures were obtained from all febrile patients on admission to the study and were handled by the microbiology laboratory in the usual fashion (Bactec; Johnston Labs, Cockeyville, Md.). Blood culture isolates were subjected to the same in vitro susceptibility testing as wound isolates.

Of the 22 patients receiving cefotiam, 14 received 2 g intravenously every 12 h. Three patients received 1 g every 12 h intramuscularly, and five received the same dose by intramuscular injection. Among the 17 patients receiving cephalothin, 11 were given 1 g every 6 h intravenously, and 6 received 500 mg every 6 h, 4 by intramuscular injection. Duration of therapy ranged from 5 to 18 days with a mean of 7.4 days (7.6 days of cephalothin versus 7.18 days of cefotiam; not statistically significant). No patient received oral antibiotics after cessation of parenteral therapy. Response was defined as (i) reduction of temperature to normal, (ii) decrease of leukocyte count by 15%, (iii) resolution in the clinical signs and symptoms of bacterial infection of the skin and soft tissues, and (iv) failure to recover from specimens obtained at the site of infection upon completion of therapy the pathogen that was present on entry.

The majority of patients responded to therapy with resolution of fever (if present) and decreasing signs of skin and soft
TABLE 1. Comparative MICs of cefotiam and cephalothin against 56 aerobic isolates from skin and soft tissue infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. tested</th>
<th>Cefotiam (µg/ml)</th>
<th>Cephalothin (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range Mean</td>
<td>Range Mean</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>21</td>
<td>0.25-8.0 3.15</td>
<td>0.06-8.0 2.00</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>5</td>
<td>0.50-64.0 21.70</td>
<td>0.06-4.0 2.41</td>
</tr>
<tr>
<td>Streptococci</td>
<td>6</td>
<td>0.50-16.0 0.58</td>
<td>0.50-4.0 1.50</td>
</tr>
<tr>
<td>Enterococci</td>
<td>4</td>
<td>32.0-64.0 48.00</td>
<td>16.00-64.0 40.00</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>3</td>
<td>0.5-8.0 3.16</td>
<td>0.50-64.0 32.16</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>3</td>
<td>0.5-8.0 4.16</td>
<td>2.00-8.0 14.00</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>1</td>
<td>32.00</td>
<td>32.00</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>6</td>
<td>16.0-64.0 40.00</td>
<td>32.0-64.0 48.00</td>
</tr>
<tr>
<td><em>Protein vulgaris</em></td>
<td>1</td>
<td>8.00</td>
<td>64.00</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>4</td>
<td>2.0-64.0 25.5</td>
<td>16.0-64.0 44.00</td>
</tr>
<tr>
<td><em>Pasteurella multicide</em></td>
<td>1</td>
<td>NT*</td>
<td>NT NT</td>
</tr>
</tbody>
</table>

* NT, Not tested.

With rare exception, *Staphylococcus aureus* or streptococci were recovered from patients with skin and soft tissue infections. *Streptococcus avium* was isolated in pure culture from one patient with a foot abscess. This isolate was susceptible to cefotiam and responded clinically with complete resolution of the abscess and surrounding cellulitis. We are unaware of previous reports of skin and soft tissue infection owing to this organism. Kaye (5) states that *Streptococcus avium* probably is not pathogenic for humans. Although it is sometimes classified as an enterococcus, it belongs to the Lancefield classification group Q. That we were able to recover this organism in pure culture from an abscess suggests it may be pathogenic for humans.

The in vitro spectrum of cefotiam includes Enterobacter spp. and *Citrobacter* spp., much like that of cefamandole. Perkins et al. (10) reported 15 patients with mixed-flora skin and soft tissue infections. Although the majority of patients (12 of 15) responded to cefamandole therapy, 3 failed to respond. Our results justify the use of cefotiam as a single agent in non-life-threatening infections since all eight cefotiam patients with gram-negative bacillary cellulitis were clinically and bacteriologically cured, including the diabetic patients with nongangrenous or necrotic lesions. Pankey (9) reported three of five patients with gram-negative bacillary cellulitis who failed on amoxicillin therapy.

We found cefotiam to be a safe, well-tolerated, and effective antibiotic for skin and soft tissue infections. In contrast with the currently available first- and second-generation cephalosporins, every 12-h administration was frequent enough to achieve clinical and bacteriological cures.

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LITERATURE CITED

