Once-Daily Ceftriaxone for Skin and Soft Tissue Infections

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We prospectively compared once-daily administration of ceftriaxone with cefazolin given every 8 h for the treatment of skin and soft tissue infections. Thirty-one patients received cefazolin for a mean of 4.5 days, and 26 patients received ceftriaxone for a mean of 4.0 days. All patients had a satisfactory response. Adverse reactions were few and reversible. Ceftriaxone given as a single daily intramuscular injection is effective therapy for skin and soft tissue infections.

Ceftriaxone is a semisynthetic cephalosporin which possesses an unusually long half-life of 6 to 8 h (7). It has excellent activity against both gram-negative and gram-positive organisms, including both staphylococci and streptococci (2, 6). To determine the efficacy of once-daily ceftriaxone in the therapy of skin and soft tissue infections, we compared this new drug with standard doses of cefazolin in a randomized, prospective study.

All patients were adults hospitalized on the General Surgical Service ward of San Francisco General Hospital for therapy of cellulitis, abscesses with cellulitis, infected ulcers, or bursitis. Written informed consent was obtained from all patients according to the guidelines of the Institutional Review Board of the University of California at San Francisco and the U.S. Food and Drug Administration. Patients were excluded if they were allergic to penicillins, cephalosporins, or lidocaine; were pregnant or nursing; had severe hepatic or renal disease or underlying fatal illness; or were receiving concomitant antibiotics.

Patients were prospectively assigned to receive either ceftriaxone or cefazolin by random allocation. Ceftriaxone was administered intramuscularly at a dose of 1 g daily. The drug was mixed with lidocaine to reduce pain (7). Cefazolin was given either intramuscularly or intravenously at a dose of 1 g every 8 h. All patients evaluated received protocol therapy for a minimum of 2 days, the final duration of therapy being determined by the responsible surgeons. Surgical drainage was performed when required.

Cultures were attempted in all patients by aspiration or swabbing. Specimens were cultured aerobically, and all isolates were identified to species level. Susceptibility to both ceftriaxone and cefazolin was determined by disk diffusion. Zones of inhibition of ≥16 mm were considered indicative of susceptibility to ceftriaxone. Patients with positive initial cultures had repeat cultures, when possible, on day 4 of therapy and after therapy was completed. Patients were considered to be bacteriologically cured if the follow-up culture showed eradication of the organism or the initial lesion had healed so that no follow-up culture could be obtained. Patients were classified as a qualified cure if the original organisms were present in reduced numbers or eliminated but replaced by a new organism. Persistence of the original pathogen in high numbers signified bacteriological failure.

Patients were examined daily by a member of the Infectious Disease Service. Vital signs were recorded and lesions were evaluated for erythema, induration, and drainage. Clinical outcome was determined as follows: cure, clinical findings subsiding during observation with no remaining evidence of infection; improvement, clinical findings subsiding but incomplete resolution of signs of infection at the time the drug was discontinued; failure, no apparent response to therapy.

All patients had laboratory evaluation before therapy was begun and every 4 days during therapy. Laboratory tests included a complete blood count with differential and platelet count, urinalysis with microscopic examination, and measurements of blood urea nitrogen, creatinine, alkaline phosphatase, bilirubin, and hepatic enzymes (serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase). All patients were questioned regarding symptoms which may have been related to drug administration.

Sixty-eight patients were enrolled in the study; however, 11 were excluded from the analysis (3 receiving cefazolin and 8 receiving ceftriaxone). Ten patients were excluded because they received the study antibiotic for 1 day or less, and one individual was excluded because he was found to have acute gout rather than an infection. The median age of the 57 remaining patients was 35 (range, 19 to 83), and 82% of these patients were male. Underlying illnesses were common and included alcoholism (22), parenteral drug abuse (18), and diabetes (2). Most of the patients had cellulitis, with or without an accompanying abscess (Table 1). Approximately one-half of these patients had a temperature of ≥37.8°C or a leukocyte count of ≥10,000/μl upon admission.

Forty-four patients had a pathogen recovered from the lesion (Table 2). Eight patients had no organism isolated, and no material could be obtained for culture in five patients. The majority of isolates were gram-positive organisms; however, gram-negative aerobes were isolated as the only organism in two patients and in association with gram-posi-

Table: Clinical diagnoses in study patients

<table>
<thead>
<tr>
<th>Treatment group (no.)</th>
<th>No. of patients with following diagnosis:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cellulitis</td>
<td>Infected ulcer</td>
</tr>
<tr>
<td></td>
<td>Alone</td>
<td>With abscess</td>
</tr>
<tr>
<td>Ceftriaxone (26)</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Cefazolin (31)</td>
<td>18</td>
<td>8</td>
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</tbody>
</table>

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tive organisms in seven other patients. The treatment groups were well matched for demographic, clinical, and microbiological data (Tables 1 and 2).

Ceftriaxone was given to 26 patients for a mean of 4.5 days (range, 2 to 9 days). Twenty-four patients were cured and two patients were clinically improved at the time ceftriaxone was discontinued. All 19 patients with positive cultures had the causative organism eradicated. Cefazolin was given to 31 patients for a mean of 4.0 days (range, 2 to 7 days). Twenty-seven patients were classified as being clinically cured and four as clinically improved. All 25 patients with positive cultures had eradication of the causative organism.

Both ceftriaxone and cefazolin were well tolerated. Eosinophilia developed in three patients receiving ceftriaxone and five patients receiving cefazolin. Mild transaminase elevation (less than twice normal) occurred in three patients receiving ceftriaxone and one patient receiving cefazolin. Two individuals receiving ceftriaxone developed pyuria (5 to 10 leukocytes per high-power field) which disappeared when therapy was discontinued. The patients were asymptomatic, the pyuria was not accompanied by either proteinuria or hematuria, and no change in renal function occurred.

Oral therapy will suffice for the majority of patients with skin and soft tissue infections. When hospitalization and parenteral therapy is required, customarily either a beta-lactamase-resistant penicillin or a first-generation cephalosporin has been used. Recently a number of second- and third-generation cephalosporins have also been shown to be effective in treating such infections (4, 5, 10). Ceftriaxone is unique among the currently available cephalosporins because of its very long half-life of 6 to 8 h in serum, which permits infrequent drug administration. Ceftriaxone has previously been shown to be effective when given every 12 h for serious infections (3). The present study demonstrates that as little as 1 g given as a single daily dose was effective therapy for skin and soft tissue infections requiring hospitalization. The drug was very well tolerated, with adverse reactions similar to those reported for first-generation cephalosporins (11).

Once-daily administration of anti-infectives has practical as well as economic advantages (1). The ability to give a drug intramuscularly once daily would facilitate the therapy of patients with poor venous access, such as patients receiving chemotherapy. Abusers of parenteral drugs have frequent episodes of serious skin and soft tissue infections caused by a wide variety of both gram-negative and gram-positive organisms, and they seldom have good venous access sites (12). The broad spectrum of activity of ceftriaxone and its effectiveness when given as an intramuscular injection should facilitate therapy in these very difficult patients. In addition, long dosing intervals and the intramuscular route of administration decrease the cost of antimicrobial administration in hospitalized patients (1) and may permit home therapy in selected patients (8, 9).

LITERATURE CITED


TABLE 2. Bacteriological diagnosis in study patients

<table>
<thead>
<tr>
<th>Treatment group (nos.)</th>
<th>Streptococci</th>
<th>Staphylococcus aureus</th>
<th>Aerobic gram-negative bacilli</th>
<th>No organism isolated</th>
<th>No culture material obtained</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group F</td>
<td>Group A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone (26)</td>
<td>1</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cefazolin (31)</td>
<td>0</td>
<td>7</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

* Two patients with Klebsiella pneumoniae, one each with Enterobacter agglomerans and Acinetobacter calcoaceticus, and three with multiple isolates.

* Escherichia coli and Haemophilus influenzae.