Clinical Comparison of Piperacillin and Cefoxitin in Patients with Bacteriologically Confirmed Infections

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The objective of this double-blind study was to compare the efficacy and safety of piperacillin with that of cefoxitin in patients with bacterial infections. Seventy-five hospitalized patients were treated with intravenous piperacillin (18 g/day) or cefoxitin (12 g/day) for a mean period of 11.5 days. Multiple serious underlying conditions were present in 91% of the patients in both treatment groups. The infection sites were the respiratory, urinary, and gastrointestinal tracts, the skin and skin structures, and the bones. Among the patients with evaluated courses of therapy, 87% (20 of 23) of the patients in the piperacillin-treated group and 90% (19 of 21) of the cefoxitin-treated patients were cured or improved. Multiple sites of infection were present in 6 patients given piperacillin and in 11 patients given cefoxitin. Gram-negative aerobic bacteria were the most frequently isolated organisms (56% of isolates). In each treatment group, 91% of the pathogens were eradicated. Three piperacillin-treated patients (9%) and four cefoxitin-treated patients (11%) had adverse clinical effects related to therapy; most of the effects were moderate in intensity. In conclusion, both piperacillin and cefoxitin were clinically safe and effective antibiotics for the treatment of these patients, most of whom had severe underlying conditions.

Interest in the use of parenteral penicillins for the treatment of patients with bacterial infections has recently increased because of the synthesis of different forms of this type of antibiotic. One new penicillin, piperacillin, has an extended in vitro spectrum of activity, which includes both gram-negative and gram-positive aerobic and anaerobic bacteria (1–3, 5). Several clinical studies have indicated the usefulness of piperacillin in patients with infections caused by susceptible organisms (6, 7, 12, 13). Based on these results, the present double-blind study further explored the usefulness of piperacillin and compared its clinical efficacy and safety with those of cefoxitin in patients with bacterial infections.

MATERIALS AND METHODS

Patient selection. Hospitalized adults were enrolled in the study if they showed strong presumptive signs of bacterial infection in the respiratory tract, the skin and skin structures, the urinary tract (100,000 bacteria per ml of urine), the bones or joints, or the abdomen, including gastrointestinal and biliary tract infections. To be enrolled in the study in any one diagnostic category, a patient had to show all the signs and symptoms of that category. These included, for respiratory tract infections, cough, sputum production, and fever; for skin and skin structure infections, purulent drainage, erythema, cellulitis, fever, and pain; for urinary tract infections, pyuria, fever, and positive urine cultures; for infections of the bones and joints, pain, effusion, fever, and swelling; and for gastrointestinal or biliary infections, abdominal pain, nausea, and vomiting. Patients were excluded for the following reasons: (i) a known hypersensitivity to any of the penicillins, cephalosporins, or cephamycins; (ii) a high probability of death within 48 h, despite planned intensive therapy; (iii) a history of resistance of the infecting pathogens to either study drug; (iv) pregnancy or lactation; (v) negative pretherapy cultures; (vi) the concurrent administration of effective antimicrobial therapy; (vii) a need for systemic antimicrobial drugs other than the study medications during the trial; (viii) a need for concomitant probenecid therapy; (ix) underlying illness or other circumstances making the planned therapy and follow-up unlikely to be completed; and (x) the presence of infected surgical devices. All of the patients who entered the study signed a statement giving informed consent.

Medication. Treatment was initiated as double-blind therapy according to a stratified randomization schedule. Piperacillin and cefoxitin were administered by 30-min intermittent intravenous infusions. The daily dose for piperacillin was 18 g, given in partial doses four times a day; the daily dose for cefoxitin was 12 g, also given in partial doses four times a day. The protocol required that the study antibiotics be administered for at least 5 days. Other systemic antimicrobial medication that would interfere with the evaluation of the efficacy of the study antibiotics was not permitted.

Clinical evaluations. Before a patient entered the study, a complete medical history was obtained, underlying diseases were recorded, and a physical examination was performed. During the administration of the study drugs, vital signs were closely monitored, and body temperature was recorded every 4 to 6 h. The patients were examined daily to document the clinical course of the infection, and other examinations and evaluations, such as X rays, were conducted as necessary.

Bacteriologic evaluation. Specimens of blood and, when possible, specimens from infected sites were cultured for aerobic and anaerobic organisms before the start of treatment, during treatment (2 to 4 days after the initiation of therapy), and at the end of treatment (24 to 72 h after the end of therapy). Urine cultures for patients with urinary tract infections (all of whom had initial counts of 100,000 bacteria per ml of urine) were repeated 5 to 9 days after therapy was discontinued and again 4 to 6 weeks later. Additional specimens for culture were obtained as required. Each organism isolated was tested for susceptibility to the study drug by the
standard disk diffusion and agar or broth dilution procedures.

Criteria for clinical and bacteriologic responses. The clinical response to therapy was based on the subjective response of a patient, the physical examinations, the X-ray findings, and the results of laboratory tests, excluding bacteriologic examinations. The four classes of this response were defined as follows. (i) For a cure, clinical findings subsided completely, with no evidence of infection at the time treatment was completed or during follow-up studies. (ii) For an improvement, clinical findings subsided significantly but with incomplete resolution of evidence of infection. (iii) For a relapse, clinical improvement was followed by deterioration during follow-up. (iv) For a failure, there was no demonstrable response to therapy. The response was then evaluated without knowledge of the antibiotic that had been given.

Bacteriologic response for patients with non-urinary tract infections was based on the results of cultures taken before, during, and after therapy. The following definitions were used. Eradication was the absence of the original pathogen(s) at the posttherapy follow-up. Marked reduction was a decrease in the number of organisms to a clinically insignificant level in the posttreatment culture. Persistence was the presence of the original pathogen in the posttherapy culture or in the final culture when treatment was discontinued because of lack of response. Multiple response was the presence of two or more pathogens and a different response for each organism. Indeterminate evaluations were the result of death or conflicting concomitant antibiotic therapy.

For patients with urinary tract infections, the bacteriologic response was defined as either short- or long-term as follows. A short-term cure was indicated by a negative culture during therapy and up to 5 to 9 days after therapy; a short-term failure was indicated by an initial pathogen present during treatment or up to 5 to 9 days after therapy or both; and a short-term superinfection was indicated by new pathogens isolated during therapy or 1 to 9 days after treatment. A long-term cure was indicated by a negative culture during therapy and at 4 to 6 weeks after therapy; a long-term recurrence (relapse) was indicated by a short-term cure with reisolation of the original organism before or at the 4- to 6-week follow-up visit; and a long-term reinfection was indicated by a short-term cure with isolation of a new pathogen before or at the 4- to 6-week follow-up.

Safety evaluation. Clinical laboratory tests were performed for each patient before, during, and after therapy. These included hematologic tests (hemoglobin, hematocrit, leukocyte count, differential count, and platelet count), blood chemistry determinations (blood urea nitrogen, total bilirubin, alkaline phosphatase, serum glutamic oxaloacetate transaminase, serum glutamic pyruvic transaminase, serum creatinine, potassium, chloride, sodium, and Coomb's direct and indirect tests), and urinalysis (specific gravity, pH, albumin, acetone, glucose, erythrocytes, leukocytes, bacteria, and casts). If the patient's condition was judged to be improved or unchanged, the dose of the study drug was continued. The severity of the change, the action taken, and the outcome were included in the record of the patient. Each injection site was examined daily for signs of erythema, induration, or thrombophlebitis, and the patients were questioned about pain at the injection site. The results of these examinations were recorded. A record was kept of all adverse clinical experiences, whether observed by the physician or reported by the patient. The details recorded included the intensity of each occurrence, the action taken, the outcome, and the part played by the study drug.

Statistical analysis. For the detection of a difference between the two groups of patients at the 5% level of significance with a power of 80% (4), the study would theoretically have to include 88 patients.

RESULTS

Seventy patients (43 men and 27 women) were enrolled in the study. The age range for the 35 patients who received piperacillin was 20 to 88 years (mean, 64 years), and that for the 35 patients who were given cefoxitin was 25 to 85 years (mean, 63 years). Sixty-nine percent (48 of 70) of the patients were 60 years of age, and 39% (27 of 70) were over 70 years old. Data for 25 patients were excluded from the efficacy analysis because the patients did not meet the protocol standards. Thus, 44 patients were included in the efficacy analysis (23 in the piperacillin-treated group and 21 in the cefoxitin-treated group), and all 70 patients were included in the safety analysis.

Dosage and duration of therapy. Both antibiotics were administered intravenously as described above. The dosage range of piperacillin was 147 to 460 mg/kg per day; the dosage range of cefoxitin was 139 to 253 mg/kg per day. The patient who received 460 mg of piperacillin per kg per day weighed 86 pounds (39.09 kg). The mean duration of treatment was 11 days (range, 5 to 19 days) for the 23 piperacillin-treated patients and 12 days (range, 5 to 31 days) for the 21 cefoxitin-treated patients.

Patient characteristics. Multiple underlying conditions were present in 91% of the patients in both treatment groups. The conditions most frequently present were cardiovascular disease (56 of 70 patients, or 80%), chronic obstructive pulmonary disease (14 of 70 patients, or 20%), alcoholism and its sequelae (14 of 70 patients, or 20%), gastrointestinal disorders (14 of 70 patients, or 20%), and diabetes mellitus (10 of 70 patients, or 14%). Among the patients with evaluable courses of therapy, serious underlying conditions were present in all of the piperacillin-treated patients and in 91% (20 of 22) of the cefoxitin-treated patients. The underlying disease was ultimately fatal in 23% (8 of 35) of the patients in the piperacillin-treated group and in 34% (12 of 31) of those in the cefoxitin-treated group.

Seven patients in the group given piperacillin and three in the group given cefoxitin had received antimicrobial therapy for their infection within the 2 weeks immediately preceding the study. None of the seven had received effective treatment within 3 days prior to entering the study. Concomitant antimicrobial medication was administered during the study to 3 of 23 piperacillin-treated patients and to 2 of 21 cefoxitin-treated patients. These medications included isoniazid, rifampin (2 days), mycostatin, nystatin, bacitracin, and azulfidine. These medications were judged ineffective for the purpose of this study.

Clinical efficacy. The clinical response in patients given the evaluated course of therapy is shown in Table 1. Cure or improvement was seen in 87% (20 of 23) of the piperacillin-treated patients and in 90% (19 of 21) of the cefoxitin-treated patients. Clinical failure occurred in three piperacillin-treated patients, all of whom had multiple underlying conditions (Table 1). The patient with pneumonia caused by a persistent strain of Serratia marcescens did not improve after 5 days of therapy, and treatment with piperacillin was therefore discontinued. Patient 2, with an intraabdominal abscess which developed after gastric biopsy and which was
TABLE 1. Clinical response in patients treated with piperacillin or cefoxitin

<table>
<thead>
<tr>
<th>Infection site</th>
<th>No. of patients with:</th>
<th>Piperacillin</th>
<th>Cefoxitin</th>
<th>Piperacillin</th>
<th>Cefoxitin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cure or improvement</td>
<td>Relapse or failure</td>
<td>Not assessed</td>
<td>Cure or improvement</td>
</tr>
<tr>
<td>Evaluated courses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Skin and skin structure</td>
<td></td>
<td>8</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td>4</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal and intra-abdominal abscess</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonevaluated courses</td>
<td></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Skin and skin structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Twenty-six patients (84%) were cured or improved in the piperacillin treatment group.
* Five patients (16%) relapsed or experienced treatment failure in the piperacillin treatment group.
* Six patients (19%) relapsed or experienced treatment failure in the cefoxitin treatment group.
* One patient died before response could be evaluated.
* No pathogen was isolated in one patient.
* One patient had fewer than five days of treatment.

caused by a persistent group D streptococcus, showed no improvement after 17 days of therapy because adequate drainage was not achieved; once drainage was established, improvement occurred. For patient 3, who had chronic gangrene of the big toe from which five organisms were isolated, therapy with piperacillin for 17 days was ineffective; after amputation, the site slowly healed. This patient also had congestive heart failure, hypothyroidism, rheumatoid arthritis, and previous surgery to resect an aneurysm; in addition, she had a wound infection and a urinary tract infection, both of which were cured.

The cefoxitin-treated group included three clinical failures. Two of the patients had multiple sites of infection and multiple underlying diseases. One patient, a diabetic with osteomyelitis of the big toe caused by Proteus mirabilis, as well as a skin ulcer (caused by two other organisms), was treated for 31 days. Although the skin ulcer was cured, the osteomyelitis showed no change; a suprainfection with Enterobacter cloacae developed in the toe, and amputation was necessary. The patient with pneumonia and underlying chronic obstructive pulmonary disease was treated with cefoxitin for 8 days, leading to eradication of the original pathogen (Streptococcus pneumoniae); however, suprainfection with Pseudomonas aeruginosa occurred, and the patient died of infection 1 day after cefoxitin therapy was discontinued. The third patient died of polymicrobial pneumonia after 2 days of cefoxitin therapy.

Two piperacillin-treated patients died during the study, one from infection (pneumonia) and one from multiple underlying conditions. Nine cefoxitin-treated patients died, two from infection (both had pneumonia) and seven from underlying diseases ($\chi^2 = 2.3, P > 0.05$).

**Bacteriologic response.** Before treatment, 46 organisms were isolated from the 23 patients given piperacillin, and 53 pathogens were found in the 21 patients given cefoxitin. The most frequently isolated organisms were Proteus spp. (18 isolates), Escherichia coli (16 isolates), streptococci (16 isolates), and Bacteroides spp. The distribution of bacteria was similar in each group. By bacterial type, gram-negative aerobic bacteria were the most numerous organisms encountered. The bacteriologic response to treatment is given by the type of pathogen in Table 2. Ninety-one percent of the organisms were eradicated in each treatment group. The persistent organisms in the piperacillin-treated patients (9% of the organisms isolated from that group) were Serratia spp., P. mirabilis, Enterococcus spp., and Bacteroides fragilis. In the cefoxitin-treated group, three isolates of P. mirabilis and one of E. coli were persistent (7% of the organisms isolated from that group).

Two patients in the piperacillin-treated group developed

**TABLE 2. Bacteriologic response to therapy with piperacillin or cefoxitin**

<table>
<thead>
<tr>
<th>Type of bacterium</th>
<th>Piperacillin treatment group</th>
<th>Cefoxitin treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eradicated</td>
<td>Markedly reduced</td>
</tr>
<tr>
<td>Aerobic Gram-negative</td>
<td>18 (90)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Aerobic Gram-positive</td>
<td>12 (92)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Anaerobic</td>
<td>12 (92)</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>
suprainfections (Candida sp. and Enterococcus sp. in urine culture). Both of these patients had urinary tract infections that were clinically cured, and the original pathogens were eradicated. In addition to the two previously mentioned patients, suprainfection with P. aeruginosa appeared in a cefoxitin-treated patient who had a relapse after initial improvement in a decubitus hip ulcer which was caused by four organisms. This patient, who had a primary diagnosis of urinary tract infection, showed improvement. The organisms persisting after treatment and the susceptibility of these strains to the treatment antibiotic showed no trend toward emergence of a given resistant strain.

Safety. Four adverse clinical experiences occurred in 3 of 35 (86%) of the piperacillin-treated patients, and five experiences were recorded in 4 of 35 (11.4%) of the cefoxitin-treated patients (Table 3). Therapy was discontinued in two patients (one had a rash, and the other had hepatitis and fever) who received piperacillin.

All of the adverse experiences encountered in the four cefoxitin-treated patients were moderate in intensity except one (reversible renal failure), which required that treatment be stopped. The patient with renal failure had received gentamicin just before the study; he was also severely anemic and dehydrated. Therapy was discontinued in the other three patients.

Thirty-three abnormal laboratory test values possibly, probably, or definitely changed by treatment were found in nine patients who received piperacillin, and seven abnormalities were found in seven patients who were given cefoxitin (Table 4). For most patients, recovery without remedial action occurred. Five cefoxitin-treated patients had elevated eosinophil counts (5 to 8%), and one patient had low hemoglobin and hematocrit values; a return to normal values occurred without remedial treatment.

### DISCUSSION

In this study, piperacillin was clinically as safe and effective as cefoxitin in the treatment of patients with a variety of bacterial infections. The clinical response here, i.e., the clinical cure or improvement in 87% of the piperacillin-treated patients and in 90% of the cefoxitin-treated patients, was somewhat lower than that reported by Najem et al. (8), who compared piperacillin and cefoxitin in a series of patients with surgical infections of the abdomen, and that reported by Sweet et al. (11), who evaluated both antibiotics in patients with obstetric and gynecologic infections. These differences are probably the result of differences in the ages of the patients in the various studies and the seriousness of the underlying diseases in this study. The results of this study contrast with those of Simon and co-workers (10), who concluded that piperacillin should not be used alone for the treatment of serious gram-negative infections because of clinical and bacteriologic response rates of 75% and 70% and the emergence of piperacillin-resistant Pseudomonas strains (9). The MIC of piperacillin is also known to be markedly affected by inoculum density, although the clinical relevance of this phenomenon is not clear (8). Gram-negative aerobic bacteria were the most frequently isolated organisms in this report, a result similar to that of the study of Winston et al. (13), who reported a preponderance of gram-negative aerobic bacteria in their patients with similar infections.


In conclusion, the results of this study support the use of piperacillin or cefoxitin as therapy for patients with serious bacterial infections caused by susceptible organisms.

### LITERATURE CITED