Comparison of Ceftazidime with Cefamandole for Therapy of Community-Acquired Pneumonia

JEANNETTE C. ENGLE, PATTI W. LIFLAND, AND CHARLES J. SCHLEUPNER

Division of Epidemiology and Virology, University of Virginia School of Medicine, and Infectious Diseases Section, Veterans Administration Medical Center, Salem, Virginia 24433

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Ceftazidime and cefamandole were compared in the treatment of pneumonia. The median MIC of ceftazidime for all Streptococcus pneumoniae (n = 17) and Haemophilus influenzae (n = 10) isolates was 0.125 µg/ml. All other isolates were inhibited by <0.5 µg of ceftazidime per ml, with the exception of a group B streptococcus (MIC = 4 µg/ml). Satisfactory clinical responses were observed in 91% (20 of 22) of cefamandole-treated patients and 85% (17 of 20) of ceftazidime-treated patients.

Ceftazidime is a broad-spectrum parenteral cephalosporin which combines a high level of resistance to µ-lactamases (14, 20) with a wide range of antibacterial activity (9, 10, 16, 19-21, 29, 30), including greater activity against Serratia sp. (20, 21, 29, 30) and enhanced antipseudomonal activity (9, 10, 20, 21, 30). Previous clinical evaluations of ceftazidime have been reported in the therapy of varied infections in a few patients each (3, 6, 22, 23). Although ceftazidime would not be considered a first-line drug for the therapy of community-acquired pneumonia, a clinical trial was designed to compare the efficacy and safety of ceftazidime to cefamandole in the treatment of such pneumonias, with particular attention directed toward secondary coagulation abnormalities (1, 4, 7, 31) and the development of resistance during therapy (24-27).

Patients were selected for the study by criteria previously published (27). Specific patient exclusion criteria included those previously published (27).

The exclusion for renal impairment was a creatinine level in serum of greater than 3 mg/dl, and the exclusion for hepatic dysfunction was a serum glutamic pyruvic transaminase level greater than 200 IU/liter or a bilirubin level greater than 3 mg/dl. Neutropenia of less than 1,000 granulocytes per mm3 was also an exclusion criterion.

Bacterial cultures required before entry into this study included aerobic and anaerobic blood cultures and an adequate specimen of lower respiratory tract secretions. Sputa and endotracheal suction specimens were required to be of group 5 quality as defined by Murray and Washington (15); if such a specimen could not be obtained, a transtracheal aspiration was performed.

Due to differences in half-lives, cefamandole was administered in doses of 1 g every 6 h, and 1 g of ceftazidime was given every 8 h (8, 12, 13, 19, 28). Both were administered by intravenous infusion.

Antibiotics were evaluated for therapeutic efficacy by clinical and bacteriological criteria as previously published (27). Colonization and superinfection have also been defined previously (27).

All bacterial isolates were initially tested for susceptibility to ceftazidime and cefamandole with 30- µg disks by the standard Bauer-Kirby disk diffusion technique (2). Additionally, agar dilution MICs of ceftazidime were determined on Mueller-Hinton agar (BBL Microbiology Systems) for all isolates by techniques described by the International Collaborative Study (5).

All gram-negative organisms isolated from lower respiratory tract specimens before or during therapy which became resistant upon subsequent culture to the therapeutic antibiotic were evaluated for induction of resistance by an adaptation of the disk induction method, using cefoxitin and either cefamandole or ceftazidime, depending upon which of the latter two antibiotics was the therapeutic agent (25).

Between May 1982 and May 1983, 58 patients were enrolled in this study, of which 42 were evaluable. Of the 16 nonevaluable patients, 13 were determined to have no pathogen on pretreatment culture, 2 had resistant organisms isolated from pretreatment cultures and 1 patient died on day 2 of therapy due to his underlying disease. All 42 evaluable patients had clinical, chest radiographic, and laboratory findings consistent with pneumonia. All patients were male, with a mean age of 63 years (range, 29 to 91 years); 94% were 50 years of age or older, and 60% had two or more significant underlying diseases, including chronic lung disease, alcoholism, and cardiovascular disease.

Table 1 lists the bacterial etiologies of the 42 episodes of pneumonia. Of these episodes, 29 could be attributed to either Streptococcus pneumoniae (15) or Haemophilus influenzae (8) or a combination of these organisms (2). Two of the remaining mixed infections involved H. influenzae, one with members of the family Enterobacteriaceae, and one with group B streptococcus. Therefore, pneumococci or H. influenzae or both were involved in 74% of the episodes of pneumonia. Four cases of pneumonia due to Streptococcus pneumoniae (either alone or in a combination with H. influenzae) were accompanied by bacteremia, as was one episode of pneumonia due to Staphylococcus aureus. Only seven of these pneumonias were attributable to individual gram-negative enteric pathogens, while one was a mixed gram-negative infection and one was due to Klebsiella pneumoniae and the group B streptococcus.

Geometric mean MICs and the range of MICs listed in Table 1 are consistent with clinically achievable levels of cefamandole and ceftazidime in serum and tissue. Of the isolates listed in Table 1, only the H. influenzae isolates required greater than 1 µg of cefamandole per ml for inhibition (MIC = 2 µg/ml for three isolates and 4 µg/ml for one isolate). All other isolates listed required <0.5 µg of
TABLE 1. Etiology and therapeutic outcome of bacterial pneumonias in patients treated with cefamandole or ceftazidime

<table>
<thead>
<tr>
<th>Bacterial etiology</th>
<th>Antibiotic</th>
<th>MIC (range)* (µg/ml)</th>
<th>No. of patients#</th>
<th>% Satisfactory responses$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Cefamandole</td>
<td>0.044 (0.0156–0.0625)$d</td>
<td>8 (1)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>0.75 (0.0625–0.25)$c</td>
<td>9 (2)</td>
<td>89</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Cefamandole</td>
<td>1.5 (0.25–4.0)</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>0.17 (0.0625–0.25)</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Cefamandole</td>
<td>0.0625</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>0.125</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Ceftazidime</td>
<td>0.1 (0.0625–0.125)</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>Cefamandole</td>
<td>1.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Cefamandole</td>
<td>1.0</td>
<td>2 (1)</td>
<td>50</td>
</tr>
<tr>
<td>Group B streptococci</td>
<td>Ceftazidime</td>
<td>4.0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Mixed</td>
<td>Cefamandole$e</td>
<td>0.8 (0.5–1.0)</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime$e</td>
<td>0.54 (0.0625–4.0)</td>
<td>1 (1)</td>
<td>100</td>
</tr>
</tbody>
</table>

* MICs are given as geometric means with ranges in parentheses; actual MICs are given for single organisms and groups of organisms with identical MICs.
# Number in parentheses denotes number of bacteremic cases.
$ Overall percentages of satisfactory responses were 91 and 85% for cefamandole and ceftazidime, respectively.
7 Mean for six of six isolates.
8 Mean for six of nine isolates.
9 One case of mixed Streptococcus pneumoniae-H. influenzae; one case of Klebsiella pneumoniae-Enterobacter aerogenes-H. influenzae; one case of Klebsiella pneumoniae-group B streptococci and one case of H. influenzae-group B streptococci. Means and ranges of MICs are given for gram-positive organisms and gram-negative organisms, respectively.
10 One case of mixed Streptococcus pneumoniae-H. influenzae with MICs given, respectively.

Ceftazidime per ml for inhibition, except the group B streptococcus, which required 4.0 µg/ml for inhibition.

Patients were treated for a mean of 12.5 days on ceftazidime and 10.5 days on cefamandole. Of 42 patients with pneumonia, 37 (88%) had a satisfactory response. Of the two treatment failures on cefamandole, one was an 80-year-old man with an underlying obstructive pulmonary carcinoma who was infected with a cefamandole-susceptible Citrobacter freundii not eradicated after 11 days of therapy. The second treatment failure occurred in a 57-year-old woman with rheumatoid arthritis whose Staphylococcus aureus isolate from an endotracheal suction sputum was not eradicated after 6 days of treatment. The etiological significance of the organism became questionable, and despite a change to triple antibiotic therapy, the patient subsequently died due to probable viral pneumonia.

The three treatment failures on ceftazidime therapy included a 57-year-old alcoholic who had chronic lung disease, congestive heart failure, and a ceftazidime-susceptible H. influenzae isolated from his sputum; this patient initially improved but relapsed on day 5 of therapy. The second ceftazidime treatment failure was a 57-year-old alcoholic whose ceftazidime-susceptible H. influenzae was eradicated but whose clinical condition did not improve, apparently due to an obstructive carcinoma. The third failure was a 68-year-old alcoholic who initially improved on ceftazidime but subsequently developed a superinfection. The initially ceftazidime-susceptible (zone size, 26 mm by Bauer-Kirby disk diffusion susceptibility testing) Pseudomonas cepacia became less susceptible (intermediate zone size, 18 mm) during therapy.

There were no systemic reactions, including fever or skin rash, or episodes of phlebitis during therapy with either antibiotic. In three of six instances for each antibiotic, the decreases of hemoglobin-hematocrit values were judged to be drug related; the remainder of these decrements were felt to be due to underlying disease. Correlation between direct Coomb's test positivity (7 of 22 treated with cefamandole, 9 of 20 treated with ceftazidime) and decreasing hemoglobin and hematocrit values was not demonstrated in all instances.

No prolongation of prothrombin times or partial thromboplastin times was observed during therapy with either antibiotic. Nephrotoxicity, hepatotoxicity, and gastrointestinal disturbances related to antimicrobial therapy were also not observed.

There were seven instances of colonization with resistant organisms during therapy with cefamandole, but no super-infection occurred; there were only two instances of colonization with resistant isolates during ceftazidime therapy, and one superinfection. This P. cepacia was unfortunately lost before disk induction testing could be performed. One patient each receiving ceftazidime and cefamandole became colonized with strains of Pseudomonas aeruginosa which demonstrated an induction of resistance of >4 mm to these respective agents when exposed to cefoxitin in the disk induction test (25).

The 88% efficacy rate of ceftazidime found in this study demonstrates its activity against community-acquired pathogens. There are inherent difficulties encountered in treating pneumonias in patients with major underlying diseases; the 9 of the 42 evaluable patients in this study who developed colonization with resistant organisms, and the 1 patient who developed a superinfection emphasize data demonstrating the emergence of resistant gram-negative organisms during therapy with newer cephalosporins (11, 17, 18, 24–26). Although ceftazidime is not indicated for the therapy of community-acquired infections, similar problems can be anticipated with its use for hospital-acquired infections. This observation with ceftazidime may have relevance to the finding of Wise et al. that serial in vitro passage of P. aeruginosa in the presence of ceftoxime and other cephalosporins results in development of resistance (32). Our population demonstrated well-recognized risk factors for colonization and superinfection, viz., age greater than 60 years, serious underlying disease, and the administration of broad-spectrum antibiotics (27a). Such complications in any setting should demand closer patient observation by the clinician when using the new cephalosporins, as well as follow-up LRT specimen cultures during therapy to monitor for new potential pathogens.
NOTES

LITERATURE CITED


