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Open Trial of Cefepime (BMY 28142) for Infections in Hospitalized Patients

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The safety and efficacy of cefepime, a new broad-spectrum, semisynthetic parenteral cephem antibiotic, were evaluated in an open trial at a single hospital. Seventy patients were treated with cefepime: 44 had lower respiratory tract infections, 4 had urinary tract infections, and 22 had skin or soft tissue infections. Of 65 clinically evaluable patients, 64 (98%) had satisfactory responses. No mortality or superinfections occurred. Of 57 respiratory and urinary tract pathogens, 54 (95%) were eradicated and 3 (5%) persisted after therapy. Five bacteremias (two with *Streptococcus pneumoniae* and one each with *Staphylococcus aureus*, *Proteus mirabilis*, and a coagulase-negative staphylococcus) were eradicated. MICs ranged from 1 to 8 μg/ml for 13 *S. aureus* and 9 *Pseudomonas aeruginosa* isolates and were less than or equal to 0.125 μg/ml for 10 streptococcal isolates. Adverse effects occurred in two patients: transient diarrhea and *Clostridium difficile* toxin in the stool in one patient and loose bowel movements and increased transaminases in the other patient. Cefepime appeared to be well tolerated in humans and was effective against a wide range of isolates, including *S. aureus* and *P. aeruginosa*.

Cefepime (BMY 28142) is a new aminothiazolemethoximino cephalosporin antibiotic with an extended spectrum of activity against gram-negative organisms, including multiantibiotic-resistant *Pseudomonas aeruginosa*, with preservation of activity against gram-positive organisms, including *Staphylococcus aureus* (1, 2–4). It is active therapeutically in mouse (3), rabbit (7), and rat (5) models of systemic infections. Cefepime pharmacokinetics are similar to those of ceftazidime (S. T. Forgue, R. R. Martin, D. J. Weidler, and R. H. Barbhaiya, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr no. 1070, 1987), as a 1-g intravenous dose in humans results in a peak level in plasma of approximately 70 μg/ml, protein binding of about 19%, a serum half-life of 2.2 h, and excretion almost entirely by the kidneys (3). The purpose of this open trial was to investigate the efficacy and safety of cefepime administered twice daily in treatment of lower respiratory, urinary tract, and skin or soft tissue infections.

(This study was presented in part at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, Calif., 23 to 26 October 1988.)

MATERIALS AND METHODS

Study group. This study was done at the Martinez Veterans Administration Medical Center after approval by its Human Subjects Committee. Patients hospitalized at the Martinez Veterans Administration Medical Center with signs or symptoms of acute urinary tract infection (cystitis or pyelonephritis), acute uncomplicated infection of the lower respiratory tract (bronchitis or pneumonia), or infection of the skin and soft tissues (cellulitis, pyoderma, ecthyma, furuncle, abscess, or postoperative wound infection) were eligible for inclusion. For inclusion, infections had to be of sufficient severity to warrant parenteral therapy but not immediately life threatening. Inclusion criteria for urinary tract infections were infection with a pathogen(s) susceptible to cefepime and ≥100,000 CFU of a pathogen per ml in urine culture. Pneumonia was diagnosed when (i) purulent sputum (>25 leukocytes and <10 squamous epithelial cells per 100× [low-power] field) was demonstrated by light microscopy and was of relatively recent onset (<14 days); (ii) bacteria were easily identified by Gram stain; (iii) nonbacterial pathogens were unlikely, as determined by history or other laboratory data (e.g., influenza, tuberculosis, or *Pneumocystis* infection); and (iv) a new lung field infiltrate was detected on chest radiograph. Bronchitis was diagnosed when there was purulent sputum but the chest radiograph did not demonstrate a new infiltrate.

Specific exclusion criteria for urinary tract infections included neurogenic bladder, surgical reconstruction of the genitourinary tract, and indwelling bladder catheter. Exclusion criteria for pulmonary infections included severe underlying pulmonary disease and pulmonary infection that would require long-term therapy to evaluate response, e.g., lung abscess. Skin infections associated with severe burns, decubitus ulcers, or allergic dermatitis were not included. Topical antibiotics were not allowed during the study period. The subject must have provided informed consent, be more than 18 years of age, be not of childbearing potential, be without serious liver (e.g., cirrhosis) or kidney (serum creatinine of ≥1.7 mg/dl) disease, and have no history of serious reactions to beta-lactam antibiotics.

Cefepime. Cefepime (cefepime with NaCl) was provided by Bristol-Myers Research Laboratories (Wallingford, Conn.) as a powder. One gram was reconstituted with 10 ml of sterile water, diluted in 50 to 100 ml of isotonic saline, and administered by intravenous infusion during a 30-min period.

Bacteriology. Susceptibility to cefepime was determined by the Kirby-Bauer disk diffusion method with 30-μg disks (BBL Microbiology Systems, Cockeysville, Md.), with a ≥15-mm-diameter zone of growth inhibition indicating susceptibility. Some isolates were tested to determine MICs by the agar dilution technique at Bristol-Myers Research Laboratories. MICs of ≤16 μg/ml indicated susceptibility. Anaerobic cultures were not obtained in this study. Specimens used for culture included expectorated sputum, clean-voided

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TABLE 1. Clinical responses to cefepime

Culture site	No. (%) of patients with response		
	Satisfactory	Failure	Unevaluable
Lung	41 (93)	1 (2)	2 (5)[a]
Skin	20 (91)	0	2 (9)[a]
Urine	3 (75)	0	1 (25)[b]

[a] Initial isolates were considered *S. aureus* resistant to cefepime (i.e., methicillin-resistant *S. aureus*) (see text).
[b] No pathogen isolated (one case).

midstream urine, and needle aspirates or swabs of skin and soft tissue infections.

Response to therapy. Patients were evaluated for efficacy and adverse reactions by standard methods that included history and physical and laboratory examination. Seven doses of cefepime had to be received for the patient to be considered for evaluation of efficacy. Cultures of clinically pertinent sites were obtained during treatment and 1 (3 for urinary tract infections) to 14 days after completion of cefepime therapy. For pneumonia, pre- and posttreatment chest radiographs were obtained.

A clinical response was considered satisfactory if all signs or symptoms of infection had resolved or improved at the time of posttreatment evaluation. The response was considered a failure when a clinical sign or symptom persisted unabated or increased or new signs or symptoms were evident at the time of posttreatment evaluation. Superinfection was diagnosed when the original pathogen had been eradicated, a new pathogen was isolated from the original site of infection, and clinical signs of infection were present. Symptoms routinely evaluated included fever; chills; pain at pertinent sites; dysuria; urinary urgency, frequency, burning and hesitancy; cough; sputum production; and dyspnea. Signs included rales; chest retractions; tachypnea; diminished breath sounds; skin ulceration, exudate, erythema, edema, odor, and induration; and lymphangitis. The symptoms and signs were evaluated at least every 3 to 4 days during cefepime treatment and were scored on a four-point scale, as follows: 1, resolved; 2, improved; 3, unchanged; 4, worse with respect to the last previous evaluation.

Bacteriologic response was classified as eradication, persistence, or relapse. For respiratory and skin infections, eradication was defined as failure to culture the pretreatment causative pathogen at posttreatment evaluation. For urinary tract infections, eradication was a sterile urine culture (10 μl plated with a loop) during days 2 to 4 of cefepime treatment and at posttreatment evaluation. Persistence was defined as presence of pretreatment pathogens in during-treatment and posttreatment cultures. Relapse was indicated when during-treatment cultures were sterile but posttreatment cultures yielded the original pathogen.

RESULTS

The large majority of patients had either respiratory infections (all bacterial pneumonias) or skin or soft tissue infections (Table 1). Of 65 clinically evaluable patients, 64 (98%) had a satisfactory response. The single failure occurred in a patient with *Enterobacter cloacae* pneumonia.

Haemophilus spp. and *Streptococcus pneumoniae* were the most common pulmonary pathogens (Table 2). Underlying diseases that predisposed to bacterial pneumonia were common, as 23 of 42 patients had chronic obstructive lung disease, 11 had congestive heart failure, 8 had cancer of the

TABLE 2. Microbiologic response to cefepime

Culture site	No. (%) of isolates			
	Eradicated	Persistent[a]	Present at relapse	Colonizing posttherapy
Lung	52 (96)	2 (4)	0	4[b]
Skin	21 (81)	5 (19)	0	1[c]
Urine	2 (67)	0 (0)	1 (33)[d]	0

[a] One skin isolate, *Alcaligenes odorans*, developed resistance to cefepime during treatment, as assessed by reduction in zone diameter from 19 to 14 mm by Kirby-Bauer testing. All other pathogens retained susceptibility to cefepime. The four other persistent skin isolates were *S. aureus*, a group B streptococcus, *Enterococcus faecalis*, and *Proteus mirabilis*. The two persistent pulmonary pathogens were *Serratia marcescens* and *P. aeruginosa*.
[b] Single isolates each of *Serratia liquefaciens*, *S. aureus*, *Enterobacter cloacae*, and *Pseudomonas maltophilia*. The latter two were resistant to cefepime, whereas the others were susceptible.
[c] *Citrobacter freundii* susceptible to cefepime.
[d] *E. coli* susceptible to cefepime in a patient with probable neurogenic bladder and no indwelling bladder catheter.

respiratory system or esophagus, 7 had diabetes mellitus, and 6 had significant neurologic disorders including hemiparesis, myasthenia gravis, and multiple sclerosis. Only two patients were considered to have no significant underlying diseases that predisposed to pneumonia. The mean ± standard deviation leukocyte count at time of enrollment in the study was 13,100 ± 5,800/mm^3; 60% had leukocytosis, and 5% had leukopenia. The mean number of lobes involved with pneumonia as assessed by chest radiograph was 1.6 ± 0.7. All but one patient with pneumonia responded favorably to cefepime treatment, with a mean score of 1.33 ± 0.4 at posttherapy evaluation and with 3.8 ± 1.5 signs and symptoms evaluated. The only clinical failure was a 61-year-old patient with multiple sclerosis and poor cough and chest wall function who developed an aspiration pneumonia due to *Enterobacter cloacae* (cefepime MIC of 0.06 μg/ml). He was dropped from the study because fever persisted despite 11 doses of cefepime, and he subsequently responded to the combination of cefotaxime and amikacin in high dosages.

Staphylococcus aureus and hemolytic streptococci were the most common pathogens isolated from skin and soft tissue infections (Table 2). Ten patients had cellulitis, four had infections associated with surgical wounds or lacerations due to trauma, two had pyoderma, two had infections associated with peripheral intravenous catheters, and two had cellulitis due to olecranon bursitis. The mean leukocyte count was 10,800 ± 420/mm^3, and 45% of patients had leukocytosis. All patients had a favorable clinical response, with a mean score of 1.33 ± 0.42 and with 4.55 ± 1.14 signs and symptoms evaluated at the time of posttherapy evaluation.

Five patients had bacteremia, and all were treated successfully with cefepime. Two patients with pneumonia had pneumococcal bacteremia, one patient each had cellulitis complicated by *S. aureus* and coagulase-negative-staphylococcus bacteremia, and one patient with a complicated urinary tract infection had bacteremia with *Proteus mirabilis*.

Five patients were unevaluable, because they received less than seven doses of cefepime. Four of these patients had pathogens that were initially considered methicillin-resistant *S. aureus*, as indicated by Kirby-Bauer testing with oxacillin disks. MICs for these isolates were shown later to be 2, 2, 4, and 8 μg/ml, and other data indicated that the results with the oxacillin disks were erroneous and that the isolates were methicillin susceptible. These four patients ultimately did

TABLE 3. Pathogens cultured before therapy with cefepime

Culture site	Pathogen (no. isolated)	
	Gram positive	Gram negative
Lung	*S. pneumoniae* (8) *Streptococcus viridans* (7) *S. aureus* (2) Other streptococcal spp. (2)	*Haemophilus* spp. (10) *P. aeruginosa* (7) *E. coli* (4) *Klebsiella* spp. (4) *Enterobacter* spp. (3) *Proteus mirabilis* (1) *Serratia marcescens* (1) *B. catarrhalis* (1) *Neisseria* spp. (4)
Skin and/or soft tissue	*S. aureus* (6) Coagulase-negative staphylococci (3) Beta-hemolytic streptococcal spp. (5)	*P. aeruginosa* (2) *Klebsiella* spp. (2) *E. coli* (1) *Haemophilus influenzae* (1) *Serratia marcescens* (1) *A. odorans* (1) *Morganella morganii* (1) *Proteus mirabilis* (1)
Urine		*P. aeruginosa* (1) *Proteus mirabilis* (1) *E. coli* (1)

well with vancomycin, nafcillin, or clindamycin. The fifth patient presented with fever, sweating, and flank pain and was enrolled as having a urinary tract infection. Since the urine culture was sterile, he was dropped from the study after one dose of cefepime. He was discovered to have pyonephrosis due to blockage of a ureter with a stone, and *Escherichia coli* was cultured from urine collected from the nephrostomy tube. He responded well to other antibiotics and nephrostomy drainage.

The microbiologic responses are summarized in Tables 2 and 3. *Haemophilus* spp. (10 cases) and *S. pneumoniae* (8 cases) were the most frequent respiratory pathogens. Recovered less frequently were *S. aureus* (2 cases); *Pseudomonas aeruginosa* (7 cases); *E. coli* (4 cases); *Klebsiella* spp. (4 cases); *Neisseria* spp. (4 cases); *Enterobacter* spp. (3 cases); and *Proteus mirabilis*, *Serratia marcescens*, and *Branhamella catarrhalis* (1 case each). *S. aureus* and beta-hemolytic streptococci were the most frequent skin and soft tissue pathogens. The MIC ranges (micrograms per milliliter) for all pathogens were as follows: *S. aureus*, 2 to 8 (n = 13); coagulase-negative staphylococci, 0.5 to 16 (n = 5); *S. pneumoniae*, 0.015 to 0.125 (n = 5); beta-hemolytic streptococci, 0.03 to 0.125 (n = 5); *Enterococcus* spp., 16 to 128 (n = 3); *P. aeruginosa*, 1 to 8 (n = 9); *E. coli*, 0.03 to 0.5 (n = 5); *Proteus mirabilis*, 0.06 to 8 (n = 4); *Klebsiella* spp., 0.03 to 0.5 (n = 4); *Serratia* spp., 0.125 to 4 (n = 3); *Enterobacter* spp., 0.03 to 0.5 (n = 3).

Follow-up cultures were obtained in all patients with urinary tract infections, 65% of patients with skin and soft tissue infections, and 83% of patients with pneumonia. In cases of patients who did not have follow-up cultures, either they were unable to produce purulent sputum or their skin disease had resolved. The relatively high numbers of persistent isolates in skin and soft tissue infections were due entirely to three patients with chronic skin defects that were cultured although signs or symptoms of infection were absent or substantially diminished. The single relapse occurred in a quadriparetic patient with a urinary tract infection, who may have had a neurogenic bladder but did not have an indwelling bladder catheter. *E. coli*, the original pathogen, was cultured in urine obtained 8 days after completion of cefepime treatment. This patient had no signs or symptoms of infection other than recurrent pyuria at the time of posttreatment culture and evaluation.

Five patients were colonized with potential pathogens as judged by cultures obtained 1 to 9 days after the end of cefepime treatment. No clinical superinfections were observed.

Only two patients were judged to have adverse reactions to cefepime. One patient treated for cellulitis had transient diarrhea on day 6 of cefepime therapy. Cefepime was stopped on day 10 with clinical and microbiologic cure. *Clostridium difficile* toxin (latex test) was detected in his stool, but since the diarrhea had resolved within 1 day, he was not treated for *C. difficile* diarrhea. In the other case, that of a patient with pneumonia, the serum glutamic pyruvic transaminase rose from an initial level of 42 IU/dl to 110 IU/dl on day 5 of cefepime therapy, and he had transient (1-day) loose bowel movements. He did not participate in follow-up. Of note, no effect of cefepime treatment on prothrombin times was detected.

DISCUSSION

This study indicates that cefepime is effective in pneumonia (predominantly community-acquired), skin and soft tissue infections due primarily to staphylococci and streptococci, and urinary tract infections at a dosage of 1 g every 12 h. Moderately severe infections were selected, since cefepime had not been used therapeutically in humans before. Cefepime was well tolerated, with only two minor adverse reactions.

The only clinical failure occurred in a patient with poor respiratory clearance mechanisms and a pneumonia due to *Enterobacter cloacae*. This patient subsequently responded to high dosages of cefotaxime in combination with amikacin. Possibly the dose of cefepime was too low or a synergistic combination of antibiotics was needed to successfully treat this patient. Two other patients in this study with *Enterobacter* pulmonary infections (one each with *Enterobacter cloacae* and *Enterobacter aerogenes*) were treated successfully with cefepime. Cefepime has bactericidal activity against most susceptible isolates, and its MICs for 90% of isolates against *Enterobacter* spp. are much lower than those of ceftazidime, cefotaxime, cefoperazone, and moxalactam (1, 3, 4).

Cefepime possesses attractive properties in comparison with other new broad-spectrum cephalosporins. Cefepime maintains bactericidal activity against methicillin-susceptible *S. aureus*, along with broad activity against members of the family *Enterobacteriaceae* and *P. aeruginosa* (1, 2–4). Cefepime resists hydrolysis by a number of purified β-lactamases (3) and has poor affinity for β-lactamases (6; Forgue et al., 27th ICAAC). As a result, cefepime has potent activity against organisms resistant to other broad-spectrum cephalosporins (Forgue et al., 27th ICAAC). The encouraging pharmacokinetics, in vitro microbiologic properties, and animal and now human therapeutic results with cefepime support its further development.

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