ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1991, p. 2371–2374
0066-4804/91/112371-04$02.00/0

Vol. 35, No. 11

Randomized Comparison of Cefepime and Ceftazidime for Treatment of Skin, Surgical Wound, and Complicated Urinary Tract Infections in Hospitalized Subjects

LAYNE O. GENTRY[1]* AND GUILLERMO RODRIGUEZ-GOMEZ[2]

St. Luke's Episcopal Hospital and Department of Microbiology and Immunology, Baylor College of Medicine, Houston, Texas 77030,[1] and Hospital Mexico, San Jose, Costa Rica[2]

Received 25 April 1991/Accepted 11 September 1991

We undertook a prospective, randomized open comparison of the broad-spectrum cephalosporins cefepime and ceftazidime in treatment of hospitalized subjects with skin or wound infections and complicated nosocomial urinary tract infections. Cefepime treatment (dosage, 2.0 g intravenously twice daily for 4 to 28 days) was successful in 36 (90%) of 40 infections of the skin and skin structure or wounds and in 16 (84%) of 19 nosocomial urinary tract infections. Ceftazidime treatment, 2.0 g every 8 h, was successful in 34 (96%) of 36 infections of the skin and skin structure and in 15 (88%) of 17 urinary tract infections. Microbiological eradication rates of each agent overall and for *Pseudomonas aeruginosa* were greater than 90%. In the cefepime group, one death occurred, contributed to by an enterococcal superinfection acquired during study drug therapy, and there were two mild and transient adverse experiences observed. Cefepime was comparable to ceftazidime in treatment of infections of the skin and skin structure requiring hospitalization and of complicated nosocomial urinary tract infections.

Cefepime, a novel alpha-methoxyimino aminothiazolyl cephalosporin, is active in vitro against many gram-positive and gram-negative bacteria which are responsible for serious infections (1, 2). Of particular interest are compelling in vitro data establishing that cefepime is active against *Pseudomonas aeruginosa* (4, 8) and more active than established broad-spectrum cephalosporins against multiply resistant strains of the family *Enterobacteriaceae* (3, 5–7); these pathogens tend to be overwhelming producers of β-lactamases, for which cefepime has a low affinity and is resistant to hydrolysis. We undertook an open, randomized comparison of cefepime and ceftazidime in treatment of bacterial infections of the skin and skin structures and urinary tract in hospitalized subjects.

MATERIALS AND METHODS

Eligible patients for study enrollment included adults hospitalized in St. Luke's Episcopal Hospital, Houston, Tex., or Hospital Mexico, San Jose, Costa Rica, with culture-proven infections due to bacteria susceptible to both cefepime and ceftazidime. Included were infections of the skin or skin structures which required hospitalization for therapy and complicated nosocomial infections of the urinary tract which required antibiotic therapy because of fever, positive cultures, and the absence of another identified source of infection. For the purposes of this study, "complicated" was defined to be the presence of an indwelling catheter or obstructive uropathy. Exclusion criteria included pregnancy or lactation, history of serious penicillin or cephalosporin hypersensitivity, anuria or a need for dialysis, granulocyte count of less than 500 mm^3, human immunodeficiency virus seropositivity or the presence of a terminal illness, and the likelihood of concomitant or extended (greater than 28 days) regimens of antibiotics (especially patients with burns, vascular or orthopedic prostheses, or possible osteomyelitis).

As originally approved by the Institutional Review Board of Baylor College of Medicine, this protocol was designed to include eligible subjects with pneumonia and/or bacteremia as well. During the time period of this study, however, we experienced competition with other departments for eligible patients with these infections, and thus enrollment was restricted.

Informed consent was provided. Enrolled subjects provided a medical history and were examined. The following types of laboratory studies were performed: hematology (hemoglobin, hematocrit, leukocyte count, platelet count, erythrocyte sedimentation rate, prothrombin time, and partial thromboplastin time), serum chemistries (serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, alkaline phosphatase, blood urea nitrogen, creatinine, glucose, sodium, potassium, calcium, and phosphorous), and urinalysis (specific gravity, pH, albumin, glucose, and microscopic examination). Prior to drug therapy, all abscesses were drained and any necessary debridement to ensure adequate tissue healing was done. Cultures were taken from the site of infection, blood cultures were performed if bacteremia was suspected, and anaerobic cultures were performed if the clinical criteria for anaerobic bacterial infection were present. For skin or wound infections, specimens were obtained by aspiration or deep swab. Those bacteria originally isolated from skin or soft tissues were considered to be pathogenic. Quantitative urine cul-

TABLE 1. Subject groups

Treatment	Avg. subject age (yr)	No. of subjects		
		Total	Male	Female
Cefepime	52.2	59	38	25
Ceftazidime	50.0	53	35	18

* Corresponding author.

TABLE 2. Subject responses to study drug therapy

Diagnosis	No. of patients treated with: Cefepime[a] with: Cure	Failure	Ceftazidime[b] with: Cure	Failure	P	95% Confidence interval (%)
Skin or wound infections	36	4	34	2	0.68	(−10, 19)
Surgical wounds[c]	22	2	24	1		
Ulcer	8	2	4	1		
Abscess	4	0	5	0		
Cellulitis	2	0	1	0		
Complicated UTI[c]	16	3	15	2	1.0	(−24, 32)
Total(%)	52 (88)	7 (12)	49 (92)	4 (8)		

[a] Two patients had adverse experiences (i.e., increased serum creatinine and diarrhea); one patient died because of overwhelming sepsis.
[b] No patients had adverse experiences, but two patients died because of aspiration pneumonia and aspiration.
[c] Infections were nosocomial.

tures were performed, with >100,000 CFU of an organism per ml defined as significant. Under this protocol we made no distinction between superinfection and colonization in terms of reporting, although study drug therapy was to be discontinued in the presence of resistant organisms determined to be pathogenic. Study drug therapy was continued for superinfections if the organisms were susceptible in vitro to the study drug or if in the opinion of the investigator and the microbiology laboratory any new resistant organisms were not causing infection, as might be the case with rare enterococci, anaerobes, or fungi.

TABLE 3. Bacteriology of skin and skin structures and surgical wounds

Source and pathogen	No. of patients treated with: Cefepime (n = 40), infection: Eradicated	Persistent	Ceftazidime (n = 36), infection: Eradicated	Persistent
Primary infection				
E. coli	10	1	10	0
P. aeruginosa	9	1	5	1[a]
Enterobacter sp.	7	0	3	0
Klebsiella sp.	4	0	5	0
Proteus sp.	5	1	2	0
Staphylococcus aureus	3	0	4	1
Acinetobacter sp.	3	0	6	0
Serratia sp.	4	0	1	0
Citrobacter sp.	2	0	3	0
Total (%)	47 (94)	3 (6)	39 (95)	2 (5)
Superinfection or colonization[b]				
Acinetobacter sp.	1	0	2	0
S. aureus	0	0	2	0
Enterococcus sp.	2	0	0	0
Pseudomonas sp.	2	0	0	0
Enterobacter sp.	0	0	2	0
Candida sp.	1	0	0	0
Total (%)	6 (15)	0	6 (17)	0

[a] One subject had rare *P. aeruginosa* in the wound after successful treatment.
[b] All new organisms isolated during study drug therapy.

TABLE 4. Bacteriology of urinary tract

Type and pathogen	No. of patients treated with: Cefepime (n = 19), infection: Eradicated	Persistent	Ceftazidime (n = 17), infection: Eradicated	Persistent
Original				
E. coli	4	0	7	0
Klebsiella sp.	3	0	4	1
Serratia sp.	3	0	4	0
Proteus sp.	4	0	1	0
P. aeruginosa	2	0	2	0
Enterobacter sp.	1	0	0	0
S. aureus	1	0	0	0
Citrobacter sp.	1	0	0	0
Morganella sp.	0	0	1	0
Total (%)	19 (100)	0	19 (95)	1 (5)
New[a]				
P. aeruginosa	1	0	0	0
Enterococcus sp.	1	0	1	0
E. coli	1	0	0	0
Total (%)	3 (16)	0	1 (6)	0

[a] Includes superinfections during therapy or reinfection with a different pathogen 2 to 6 weeks following therapy.

All bacteria isolated during the study were tested for susceptibility to cefepime and ceftazidime. Organisms were defined as susceptible to cefepime when the MIC was ≤8 μg/ml or the zone diameter resulting from a 30-μg disk was ≥19 mm, as moderately susceptible to cefepime when the MIC was 16 μg/ml or the zone diameter was 16 to 18 mm, or as resistant to cefepime when the MIC was ≥32 μg/ml or the zone diameter was ≤15 mm. Standard susceptibility criteria for ceftazidime were used. Organisms were defined as susceptible to ceftazidime when the MIC was ≤8 μg/ml or the zone diameter resulting from a 30-μg disk was ≥18 mm, as moderately susceptible to cefepime when the zone diameter was 15 to 17 mm, or as resistant to cefepime when the MIC was >16 μg/ml or the zone diameter was ≤14 mm.

Cefepime was given as 2.0 g intravenously every 12 h (q12h), while ceftazidime was given as 2.0 g intravenously q8h. Concentrations of the study drugs in serum were not measured. The study protocol permitted a reduction in dosages in cases of impaired renal function. For cefepime, the adjusted dosage was 2.0 g q24h for subjects with creatinine clearance (CC) of 31 to 50 ml/min and 1 g q24h for CC of ≤30 ml/min, while for ceftazidime the adjusted dosage was 2 g q12h for CC of 31 to 50 ml/min, 2.0 g q24h for CC of 16 to 30 ml/min, and 1 g q24h for CC of ≤15 ml/min. The minimum length of antibiotic therapy to be considered evaluable for the analysis of efficacy was 4 days, 10 days of therapy was considered standard, and a maximum of 28 days was allowed to achieve a cure. Study drug therapy was terminated upon clinical cure, isolation of a pathogen resistant to cefepime or ceftazidime, poor clinical response, intercurrent illness, or a serious adverse experience considered to be at least possibly related to study drug therapy. Whenever possible, indwelling urinary catheters were removed during study drug therapy for urinary tract infections (UTIs).

TABLE 5. Cefepime therapy failures

Infection type and subject[a]	Infection location	Pathogen	Treatment length (days)	Infection status at end of treatment	Follow-up[b]
Skin or wound					
85F	Wound	*P. mirabilis, E. coli*	14	Eradicated	Superinfection on day 6 with resistant *Enterococcus* sp. which persisted; died 29 days posttreatment because of multiple organ failure from deep tissue and bone infection
48F	Ulcer	*Proteus vulgaris*	15	Persisted	AODM; superinfection on day 15 with resistant *Acinetobacter* sp.; successfully treated with amikacin
26F	Wound	*P. aeruginosa*	9	Relapsed	Relapsed 4 days posttreatment; successfully treated with ciprofloxacin
63M	Ulcer	*Serratia* sp.	11	Eradicated	AODM; superinfection on day 11 with resistant *Pseudomonas maltophila*; successfully treated
UTI					
53F	Urinary tract	*P. aeruginosa*	12	Eradicated	AODM; reinfection 33 days posttreatment with *E. coli*
41F	Urinary tract	*E. cloacae*	5	Eradicated	Treatment discontinued because of no intravenous site; reinfection 30 days posttreatment with *P. aeruginosa*; successfuly treated
44F	Urinary tract	*P. aeruginosa*	13	Eradicated	Reinfection with *Enterococcus* sp.; successfully treated with ampicillin

[a] Subject designations indicate the patient's age (in years) and sex (M, male; F, female).
[b] AODM, adult onset diabetes mellitus.

Subjects were evaluated on study day 3 to 5 and at the completion of therapy. Follow-up evaluations (physical examination and microbiology if necessary) were performed 2 weeks following the completion of therapy for all subjects, and subjects with UTIs were further contacted by telephone 4 weeks later. Study drug therapy was judged to be a cure if there was a resolution of the clinical signs and symptoms of infection, sterilization of the end-of-treatment cultures, and no need for further antimicrobial therapy prior to follow-up. Failure denoted persistence of symptoms, including the need for further and extensive surgical debridement during study drug therapy, persistent or resistant pathogens at the site of infection, or the need for concomitant or additional antibiotic therapy during the protocol or prior to the follow-up examination.

RESULTS

There were 112 evaluable subjects; 59 received cefepime and 53 received ceftazidime (Table 1). Subjects were typically males slightly over 50 years old. Diagnoses included nosocomial surgical wound infection, community-acquired cellulitis, infected ulcer and abscess, and nosocomial complicated UTI (Table 2). No subject enrolled in this study had confirmed bacteremia (four of four positive blood cultures). Cefepime therapy was successful for 52 (88%) of 59 subjects, while ceftazidime treatment was successful in 49 (92%) of 53 subjects. Clinical response rates were comparable for skin or wound infections (90% success for cefepime and 94% for ceftazidime, $P = 0.68$, Fischer's exact test) and UTIs (84% for cefepime and 88% for ceftazidime, $P = 1.0$, Fischer's exact test). As the ceftazidime success rates were uniformly,

TABLE 6. Ceftazidime therapy failures

Infection type and subject[a]	Infection location	Pathogen	Treatment length (days)	Infection status at end of treatment	Comments
Skin or wound					
77M	Wound	*E. coli*	9	Eradicated	Superinfection on day 5 with resistant *E. cloacae*; successful debridement; no further antibiotic treatment
49M	Wound	*E. coli*	8	Eradicated	Superinfection on day 5 with susceptible *Acinetobacter* sp. which persisted; successfully treated with trimethoprim-sulfamethoxazole
UTI					
56M	Urinary tract	*S. marcescens*	11	Eradicated	Reinfection 9 days posttreatment with *Enterococcus* sp.; no further antibiotics; died 17 days posttreatment because of aspiration via tracheo-esophageal fistula
40M	Cystitis	*Klebsiella pneumoniae*	13	Relapsed	Relapse 9 days posttreatment; successfully treated with nitrofurantoin

[a] Subject designations indicate the patient's age (in years) and sex (M, male).

albeit only slightly, higher, type II error analysis was indicated. The statistical powers for the observed differences with this sample size were only 9% for skin or wound infections and 5% for UTIs, the sample sizes needed to achieve 80% power would have been 1,442 and 2,360 subjects, respectively, and the 95% confidence intervals for the differences in cure rates for ceftazidime and cefepime were, respectively, −10 and 19% for skin or wound infections and −24 and 32% for UTIs. Statistical analysis reveals and predicts no differences in the cure rates of cefepime and ceftazidime.

Both drugs were well tolerated, with only two mild adverse experiences (increased serum creatinine and diarrhea) in the cefepime group assessed to be at least possibly related to drug therapy. There were no other clinically significant changes observed during the study. No subject failed to receive the minimum 4 days of antibiotic therapy. For three subjects in the cefepime group, the dosage was reduced to 2.0 g q24h because of impaired renal function, with the outcome a clinical cure in all three. One subject in the ceftazidime group received 2.0 g q12h and was cured.

Three subjects enrolled in the study failed to survive their hospitalization. In the cefepime group, one 85-year-old subject died because of overwhelming sepsis 2 weeks following the completion of an unsuccessful regimen of cefepime for postoperative wound infection due to *Proteus mirabilis* and *Escherichia coli*; although these initial pathogens were eradicated; a superinfection due to a cefepime-resistant *Enterococcus faecalis* strain contributed to the subject's eventual death. One 87-year-old patient was enrolled in the ceftazidime group for surgical wound infection due to *Enterobacter cloacae*, yet entry cultures subsequently grew a ceftazidime-resistant *P. aeruginosa*; despite appropriate alternative antibiotic therapy, this patient died 8 days later because of aspiration pneumonia. The other death in the ceftazidime group was due to massive intrapulmonary aspiration of gastric contents 17 days following unsuccessful ceftazidime therapy for UTI due to ceftazidime-susceptible *Serratia marcescens*.

For the 40 subjects with skin or wound infections who received cefepime, 47 (94%) of 50 pathogens were eradicated, including 9 of 10 *P. aeruginosa* strains; there were six episodes of superinfection or colonization in this group (Table 3). Among the 36 subjects with skin or wound infections who received ceftazidime, 39 (95%) of 41 pathogens were eradicated, including five of six *P. aeruginosa* strains; six episodes of superinfection or colonization accompanied ceftazidime therapy. One persistent *P. aeruginosa* strain was quantitatively rare, and further antibiotic therapy was not believed to be necessary for the affected subject.

UTIs responded well to each regimen (Table 4). In the cefepime group, all 19 initial pathogens were eradicated, whereas 19 (95%) of 20 were eradicated by ceftazidime. *Enterococcus faecalis* was responsible for a relapse of infection within 4 weeks of the end of drug therapy in one subject in each group, while *P. aeruginosa* and *E. coli* were also responsible for relapse in the cefepime group.

Listed in Table 5 are the clinical summaries for the seven subjects for whom therapy with cefepime was not successful, and in Table 6 are listed those four subjects for whom ceftazidime therapy was not successful. Within the important subgroup of diabetic subjects with infections of the skin and skin structure, we note that 9 (82%) of 11 treated with cefepime were cured by the therapy, as opposed to 5 of 5 cured with ceftazidime. For diabetic subjects with UTIs, the response was cure in four (80%) of five treated with cefepime and two of two treated with ceftazidime.

DISCUSSION

From these results, we have an early confirmation in vivo of the results of in vitro and safety studies with cefepime. Cefepime is well tolerated and appears to be comparable to ceftazidime in treatment of skin or wound infections and nosocomial UTIs in hospitalized patients. Although ceftazidime is more active in vitro against *P. aeruginosa* than cefepime is (2, 5, 7), clinical and bacteriologic responses for this pathogen were equivalent in this study. Larger studies are required to confirm the relative efficacies of cefepime and ceftazidime in diabetic subjects with infection due to *P. aeruginosa*.

Cefepime has been shown to have excellent in vitro activity against members of the family *Enterobacteriaceae*. Strains of *Enterobacter* spp., *S. marcescens*, and *Citrobacter freundii* which may be resistant to other cephalosporins such as ceftazidime and cefotaxime are frequently very susceptible to cefepime (3, 5–7). During the course of this study, one prospective subject was found to have a surgical wound infected with ceftazidime-resistant, cefepime-susceptible *Enterobacter cloacae* and was compassionately treated for 7 days with cefepime, which effected a cure of the infection. This resistant isolate was in a patient from the Hospital Mexico, San Jose, Costa Rica, study site, where ceftazidime had not been used prior to this study. There is the suggestion that plasmid mediation may not always be responsible for selective resistance to ceftazidime. These data are of great interest to us, as the *Enterobacter* spp. in our center are usually resistant to available cephalosporins such as ceftazidime. We look forward to further studies to clarify the role of cefepime in treatment of difficult infections due to gram-negative bacteria.

REFERENCES

1. **Fuchs, P. C., R. N. Jones, A. L. Barry, et al.** 1986. In vitro activity of carumonam (RO 17-2301), BMY-28142, aztreonam, and ceftazidime against 7620 consecutive clinical bacterial isolates. Diagn. Microbiol. Infect. Dis. **5**:345–349.
2. **Fuchs, P. C., R. N. Jones, A. L. Barry, and C. Thornsberry.** 1985. Evaluation of the in vitro activity of BMY-28142, a new broad-spectrum cephalosporin. Antimicrob. Agents Chemother. **27**: 679–682.
3. **Fung-Tomc, J., T. J. Dougherty, F. J. DeOrio, V. Simich-Jacobson, and R. E. Kessler.** 1989. Activity of cefepime against ceftazidime- and cefotaxime-resistant gram-negative bacteria and its relationship to β-lactamase levels. Antimicrob. Agents Chemother. **33**:498–502.
4. **Fung-Tomc, J., E. Huczko, M. Pearce, and R. E. Kessler.** 1988. Frequency of in vitro resistance of *Pseudomonas aeruginosa* to cefepime, ceftazidime, and cefotaxime. Antimicrob. Agents Chemother. **32**:1443–1445.
5. **Neu, H. C., N. X. Chin, K. Jules, and P. Labthavikul.** 1986. The activity of BMY-28142, a new broad spectrum beta-lactamase stable cephalosporin. J. Antimicrob. Chemother. **17**:441–452.
6. **Rolston, K. V. I., M. E. Alvarez, K. C. Hsu, and G. P. Bodey.** 1986. In-vitro activity of cefpirome (HR-810), WIN-49375, BMY-28142 and other antibiotics against nosocomially important isolates from cancer patients. J. Antimicrob. Chemother. **17**:453–457.
7. **Tsuji, A., A. Maniatis, M. A. Bertram, and L. S. Young.** 1985. In vitro activity of BMY-28142 in comparison with those of other β-lactam antimicrobial agents. Antimicrob. Agents Chemother. **27**:515–519.
8. **Vuye, A., and J. Pijck.** 1985. In vitro antibacterial activity of BMY-28142, a new extended-spectrum cephalosporin. Antimicrob. Agents Chemother. **27**:574–577.