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Safety and efficacy of cefepime versus ceftazidime in the treatment of severe infections

Chun-Kai Huang, Yao-Shen Chen, Susan Shin-Jung Lee, Wei-Ru Lin, Hung-Chin Tsai, Hsi-Hsun Lin, Shue-Ren Wann, Joanna Yan-Wan Chen, Muh-Yong Yen, Yung-Ching Liu

Section of Infectious Diseases, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung; and National Yang-Ming University, Taipei, Taiwan, ROC

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An open-label, randomized study was conducted to evaluate the safety and efficacy of cefepime versus ceftazidime in the treatment of severe bacterial infections, including septicemia, urinary tract infection, bacterial bronchitis, bacterial pneumonia, and intraabdominal infection. Fifty-two patients with severe infections were eligible and prospectively randomized to receive cefepime (26 patients) or ceftazidime (26 patients) during a 15-month period. Forty-two patients were evaluable (24 in the cefepime group and 18 in the ceftazidime group). Most (86%) of the patients had urinary tract infections and the most commonly isolated pathogen was *Escherichia coli* (79%). Satisfactory clinical response rates of 71% and 61%, and bacteriological eradication rates of 87.5% and 89% were achieved for the cefepime and ceftazidime groups, respectively. Two patients treated with cefepime died, one from superinfection and one from suspected paraneoplastic syndrome. Cultures of the blood obtained at entry into the study were positive in 19 (45%) of the 42 evaluable cases. In the cefepime group, a patient with *Salmonella paratyphi* A septicemia was cured, which has not been previously reported. Adverse effects attributable to therapy were minimal in both groups of patients, and none required discontinuation or dose reduction. In conclusion, these results suggest that cefepime is as efficacious and well tolerated as ceftazidime in the treatment of severe bacterial infections, such as septicemia, urinary tract infection, bacterial bronchitis, bacterial pneumonia, and intraabdominal infection.

Key words: Cefepime, ceftazidime, severe bacterial infections

Severe bacterial infection is a major cause of morbidity and mortality in hospitalized patients. Early and appropriate antimicrobial therapy can improve the outcome. However, the need to decide upon specific therapy without the benefit of a definitive etiology presents a challenge to physicians. Extended-spectrum cephalosporins have been established as safe and effective agents when given as empirical monotherapy to both neutropenic and non-neutropenic patients with severe bacterial infections [1-6]. Ceftazidime is a semisynthetic, third-generation cephalosporin with a broad spectrum of antibacterial activity and high resistance to β-lactamases. It has been used as empirical therapy for both neutropenic and non-neutropenic patients with serious bacterial infections [1-3]. It is active against *Pseudomonas aeruginosa* and other aerobic gram-negative bacilli [7]. However, this increased activity against gram-negative bacteria has been achieved at the expense of reduced activity against gram-positive bacteria. Cefepime is a parenteral, fourth-generation cephalosporin with a broader spectrum of antibacterial activity and greater activity against gram-positive bacteria than third-generation cephalosporins [8-12]. It has a low binding affinity for the major inducible chromosomally mediated β-lactamases and is resistant to hydrolysis by common β-lactamases [13-16]. It is also a poor inducer of type I β-lactamases. Its activity against streptococci (except enterococci), methicillin-susceptible staphylococci, the majority of *Enterobacteriaceae* and *Pseudomonas* species makes it particularly attractive as the management of severe infections [17]. It has been evaluated for the treatment of a variety of severe bacterial infections and produced favorable responses in many studies [18-20]. However, clinical data on cefepime use in Taiwan is limited, and only a small number of cases have been reported [4,6, 21-23]. The objective of this study was to evaluate the safety and efficacy of cefepime versus ceftazidime in the treatment of hospitalized patients with severe bacterial infections in Taiwan.

Corresponding author: Dr. Yung-Ching Liu, Section of Infectious Disease, Department of Internal Medicine, Kaohsiung Veterans General Hospital, 386, Ta-Chung 1st Road, Kaohsiung, 813, Taiwan, ROC. E-mail: ycliu@isca.vghks.gov.tw

Patients and Methods

Hospital characteristics

This open-label, randomized study evaluated the safety and efficacy of cefepime versus ceftazidime as initial therapy in the treatment of hospitalized patients with severe bacterial infections, including septicemia, urinary tract infection (UTI), bacterial bronchitis, bacterial pneumonia, and intraabdominal infection. This study was conducted at the Department of Internal Medicine of Kaohsiung Veterans General Hospital, a 1200-bed referral hospital providing primary, secondary, and tertiary care services in southern Taiwan. The study period was 15 months in total from August 1995 through October 1996.

Patient eligibility

Hospitalized patients who had given informed consent and were 18 years of age or older were eligible for the study if they had clinical evidence of septicemia or a severe bacterial infection demonstrated by (1) meeting at least 2 of the criteria for systemic inflammatory response syndrome (SIRS) defined by Bone *et al* [24], including the presence of fever or hypothermia (body temperature >38°C or <36°C), tachypnea (>20 /min while breathing spontaneously), tachycardia (>90 /min), and leukocytosis (>12 000 white blood cell /mm^3 or 10% immature neutrophils or "bands") plus (2) at least one of the following: dysuria or flank pain, chills and/or rigors, urine cultures with a colony count $\geq 10^3$ /mL, chest X-ray finding consistent with pneumonia, purulent sputum, symptoms and signs of bacterial peritonitis (including abdominal pain, tenderness, rigidity or guarding, rebound tenderness, or the absence of bowel sounds), and known positive blood culture. Patients were excluded if they had an infection caused by a pathogen known to be resistant to the study drug; had a history of a serious hypersensitivity reaction to a cephalosporin or penicillin antibiotic; were pregnant or lactating; had renal insufficiency (oliguric with a calculated creatinine clearance (CCr) of less than 11 mL/min, or required hemodialysis or peritoneal dialysis); had a leukocyte count of less than 2000 /mm^3; had a severe disease which may have limited survival during therapy and the follow-up period (including patients who were receiving aggressive life support or treatment such as ventilator support or vasopressor therapy, or who had been classified as "do not resuscitate"; were likely to require long-term (>14 days) antimicrobial therapy for the treatment of underlying infection (eg empyema, endocarditis, osteomyelitis); had hepatic disease characterized by clinical jaundice, bilirubin ≥4 mg/dL, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥4 times the upper limit of normal; had received antimicrobial therapy within 3 days before entry into the study; were likely to receive other antimicrobial drug concomitant with the study medication or before the completion of the study; or had cystic fibrosis.

Randomization and drug therapy

Patients were randomly assigned to receive either cefepime (2 g every 12 h) or ceftazidime (2 g every 8 h) intravenously after enrollment in the study. The dose of cefepime and ceftazidime was adjusted according to renal function as follows: for cefepime, if the CCr was above 31 mL/min, no dose adjustment was required, if the CCr was between 11 and 30 mL/min, the dose was reduced to 1 g daily; for ceftazidime, if the CCr was above 50 mL/min, no dose adjustment was required, if the CCr was between 31 and 50 mL/min, the dose was reduced to 1 g every 12 h, if the CCr was between 16 and 30 mL/min, the dose was reduced to 1 g daily, and if the CCr was between 11 and 15 mL/min, the dose was reduced to 500 mg daily. The duration of therapy was 10 to 14 days or 24 to 48 h after resolution of symptoms and signs of infection, with a minimum of 5 days of therapy. The therapy was modified based on the results of clinical assessment and/or pretreatment cultures at 72 to 96 h after initiating therapy. If patients improved or were in stable condition after 72 to 96 h of initial therapy, treatment was continued. However, if patients' symptoms and signs were worsened, treatment was regarded as failure and the regimen was modified. Non-study systemic antimicrobial therapies were not given during the course of the study or during the follow-up period except when the following occurred: (1) treatment failure; (2) if isolated pathogens included a methicillin-resistant staphylococci or resistant anaerobic organisms, then vancomycin and/or an antibiotic with extended anaerobic coverage (metronidazole or clindamycin) could be started at the same time as the study cephalosporin; and (3) patients required additional antibiotics for any other infections, not related to the original site of infection, which occurred subsequent to the end of treatment. Medications other than antimicrobials could be administered as indicated but had to be recorded on the case report form.

Study procedures

Within 48 h prior to enrollment, a medical history was taken, the patient was examined for symptoms and signs of infections (including vital signs), at least 2 pretreatment blood specimens or clinical specimens

from the infected site were obtained for cultures and susceptibility testing, a chest radiograph was taken for patients with suspected pneumonia or bacterial bronchitis, laboratory tests and any diagnostic studies to further define the diagnosis were done. Laboratory tests included hematology (complete blood cell with a differential count, hemoglobin, platelet count), serum chemistry (blood urea nitrogen, creatinine, ALT, AST, total bilirubin, alkaline phosphatase), and urinalysis. During treatment and follow-up within 15 days of the completion of therapy, the following procedures were performed: clinical evaluation of signs and symptoms, physical examination, bacteriologic studies, laboratory tests, diagnostic studies (eg, chest X-ray) and an assessment for clinical adverse events occurring in association with test drug administration. Patients were evaluated clinically and bacteriologically as frequently as required during the study. If symptoms or signs of infections recurred; appropriate cultures were obtained and isolated pathogens were tested for *in vitro* susceptibility to cefepime and ceftazidime. All the laboratory data were reviewed by the investigator and patients with abnormal laboratory values were retested at appropriate intervals until the values returned to their approximate baseline levels or were deemed clinically unimportant.

Early withdrawal

The following events were considered sufficient reasons for discontinuing treatment with the study medication: (1) isolation of a pathogen resistant to the assigned cephalosporin; (2) clinical response was poor according to the investigator's findings; (3) adverse events necessitated discontinuation; (4) intercurrent illness; (5) patient's decision not to continue participation; (6) administrative reasons; and (7) deterioration of renal function with a calculated CCr <11 mL/min.

Evaluation of efficacy and safety

Patients with clinical and laboratory findings consistent with severe bacterial infections who received at least one dose of the study drug were evaluated for clinical and bacteriologic response to treatment. Clinical response was the primary endpoint, while bacteriologic response was the secondary endpoint. Clinical response was assessed based on physical examination, diagnostic studies, and infection-related clinical symptoms and signs. Bacteriologic response was determined by the results of cultures obtained before treatment, during and after the completion of treatment.

The clinical response was assessed within 15 days after the last dose of the study drug. Clinical response was classified as follows: (1) Cure: all clinical symptoms and signs relevant to the original infection either resolved or improved; no new symptoms or signs relevant to the original infection were present at the time of the final post-treatment evaluation; (2) Failure: persistence, increase, or worsening of the clinical symptoms or signs of the original infection; the appearance of new clinical symptoms and signs relevant to the original infection at the end of therapy; or recurrence of clinical symptoms and signs relevant to the original site of infection at any time during the follow-up period after an initial satisfactory response at the end of drug therapy; and (3) Unable to determine: response of the original infection to therapy was considered inevaluable if there was no follow-up evaluation of clinical symptoms and signs; or any other reason for which the response could not be classified according to the response categories above (eg, protocol violation such as the concomitant use of non-study antibiotics or if the patient was withdrawn from the study before a full evaluation of response could be made).

The bacteriologic response of the original infection was categorized according to the following criteria: (1) Eradication: the pretreatment pathogen(s) was not isolated in cultures taken during or post-therapy. If follow-up cultures could not be obtained because of the absence of purulent material, microbiologic eradication was presumed; (2) Persistent: the pretreatment pathogen was present in the final post-treatment culture. Patients who had been withdrawn from the study with the last culture obtained positive for the pretherapy pathogen were categorized as having persistent infection; (3) Unable to determine: unable to evaluate the response (eg, patient was lost to follow-up, cultures not obtained). A new infection was defined as the isolation of a new pathogen from the original site of infection or any pathogen from a new site of infection. If a new infection occurred, it was classified as either occurring at the original site or a new site, as occurring during or post therapy, and as caused by a pathogen susceptible or resistant to cefepime or ceftazidime.

The clinical and bacteriologic responses of the two treatment groups were compared. All patients enrolled in the study who received at least one dose of the study drug were monitored for adverse events and local tolerance to the study drug by objective laboratory examination and clinical assessment of the symptoms and signs.

Statistical analysis

Statistical analyses were performed by Pearson's chi-square test, Fisher's exact test, and students's *t* test as

appropriate. A p value of less than 0.05 was regarded as significant. Results were analyzed by the intention-to-treat principle as well as by evaluability.

Results

During the 15-month study period, a total of 52 patients hospitalized with severe infections were enrolled into the study. Twenty-six of these patients were randomized to receive treatment with cefepime and 26 with ceftazidime. Ten patients (2 in the cefepime group and 8 in the ceftazidime group) were excluded from the final analysis due to early withdrawal. The reasons for early withdrawal were necessity for prolonged therapy over 14 days in patients with osteomyelitis (cefepime, 2; ceftazidime, 1), splenic abscess (ceftazidime, 1), and infective endocarditis (ceftazidime, 1); pseudobacteremia due to *Bacillus subtilis* with fever of unknown origin (ceftazidime, 1); isolation of *Enterococcus* as a pathogen (ceftazidime, 2); discontinuation of therapy as a result of the patient's decision (ceftazidime, 1); and UTI with no isolate (ceftazidime, 1).

Two cases in the cefepime group were inevaluable. A 56-year-old man with UTI who was being treated with prednisolone due to nephrotic syndrome was included into the cefepime group. His blood and urine cultures isolated *Salmonella choleraesuis* C1, and his symptoms and signs resolved after treatment with cefepime for 7 days. However, he required continued oral ciprofloxacin for treatment of osteomyelitis of the T-spine, and was withdrawn from the trial because of protocol violation. The second inevaluable case was a 48-year-old woman without any known underlying disease who had a history of frequent intravenous and intramuscular injection of some unidentified drugs over 10 years ago. She was admitted for intermittent fever and lethargy for 1 month and was enrolled in the study when her blood culture was reported positive for gram-negative bacilli, which was identified as *Burkholderia cepacia*. She showed a good response to cefepime treatment but was withdrawn from the trial due to protocol violation, since therapy with oral trimethoprim/sulfamethoxazole had to be given for T-spine osteomyelitis after 2 weeks of cefepime therapy. Among the 8 patients withdrawn from the ceftazidime group, 2 who had UTI were withdrawn after urine cultures isolated *Enterococcus* (considered resistant to both cefepime and ceftazidime); one patient with infective endocarditis and villous adenoma of the rectum was shifted to crystal penicillin therapy after blood cultures isolated *Streptococcus bovis* I; one patient with a diagnosis of intraabdominal infection with *Klebsiella pneumoniae* bacteremia received other antibiotics for a splenic abscess after completion of 2-weeks of ceftazidime therapy; one patient with *Salmonella paratyphi* A bacteremia required continued oral trimethoprim/sulfamethoxazole due to the complication

Table 1. Demographic and clinical characteristics of the patients

	Intention-to-treat		Completed	
	Cefepime n = 26 (%)	Ceftazidime n = 26 (%)	Cefepime n = 24 (%)	Ceftazidime n = 18 (%)
Age (years, mean ± SD)	62±15	60 ±16	63 ±16	58 ±16
Sex (M/F)	14/12	15/11	13/11	12/6
Height (cm, mean ± SD)	157± 6	160 ± 7	157 ± 6	161 ± 7
Weight (kg, mean ± SD)	56± 9	65 ±15	56 ± 10	68 ±16
Pretreatment WBC (mm^3)	14956± 7802	15439 ± 9624	15604 ± 7775	14380 ± 5309
Prior antibiotic administration	7 (26.9)	7 (26.9)	6 (25.0)	6 (33.3)
Underlying disease (no. of patients)				
Diabetes mellitus	7 (26.9)	9 (34.6)	7 (29.2)	7 (38.9)
Bronchopulmonary	5 (19.2)	3 (11.5)	5 (20.8)	2 (11.1)
Cardiovascular	12 (46.2)	7 (26.9)	10 (41.7)	6 (33.3)
Gastrointestinal	7 (26.9)	0	6 (25.0)	0
Genitourinary	12 (46.2)	6 (23.1)	11 (45.8)	4 (22.2)
Infection types				
UTI	20 (76.9)	20 (76.9)	20 (83.3)	15 (83.3)
LRI	1 (3.8)	0	1 (4.2)	0
UTI and LRI	1 (3.8)	0	1 (4.2)	0
Intra-abdominal	1 (3.8)	5 (19.2)	1 (4.2)	3 (16.7)
Salmonellosis	2 (7.6)	1 (3.8)	1 (4.2)	0
Primary bacteremia	1 (3.8)	0	0	0
Positive blood culture	14 (53.8)	10 (38.5)	12 (50.0)	7 (38.9)

Abbreviations: WBC = white blood cell; UTI = urinary tract infection; LRI = lower respiratory tract infection

Table 2. Microbiologically documented infections

	Intention-to-treat		Completed	
	Cefepime n = 26 (%)	Ceftazidime n = 26 (%)	Cefepime n = 24 (%)	Ceftazidime n = 18 (%)
No. of patients with:				
microbiologically documented infection	26 (100)	23 (88.5)	24 (100)	17 (94.4)
polymicrobial infections	4 (15.4)	3 (11.5)	4 (16.7)	2 (11.1)
No. of microorganisms				
Gram-positive				
Streptococcus group B	1 (3.8)	0	1 (4.2)	0
Streptococcus bovis I	0	1 (3.8)	0	0
Enterococcus	0	2 (7.6)	0	0
Gram-negative				
Escherichia coli	19 (73.1)	15 (57.7)	19 (79.2)	14 (77.8)
Klebsiella pneumoniae	4 (15.4)	3 (11.5)	4 (16.7)	2 (11.1)
Pseudomonas aeruginosa	1 (3.8)	0	1 (4.2)	0
Haemophilus influenzae	1 (3.8)	0	1 (4.2)	0
Proteus mirabilis	1 (3.8)	0	1 (4.2)	0
Salmonella species	2 (7.6)	1 (3.8)	1 (4.2)	0
Providencia stuartii	1 (3.8)	1 (3.8)	0	1 (5.6)
Moraxella asloensis	1 (3.8)	1 (3.8)	0	1 (5.6)
Burkholderia cepacia	1 (3.8)	0	0	0
Other bacilli	1 (3.8)	2 (7.6)	1 (4.2)	2 (11.1)

of L-spine osteomyelitis after 2 weeks of ceftazidime therapy; one patient refused further hospitalization because she had trouble sleeping at the hospital; one patient was withdrawn from the trial after her urine and blood cultures turned out to be negative; and one patient admitted for the investigation of fever of unknown origin was enrolled in the study, but was later excluded from the analysis because blood culture was positive for *B. subtilis*, which was clinically considered as a pseudobacteremia.

Forty-two patients were eligible for the final efficacy analysis. The demographic characteristics of these patients are shown in Table 1. The 2 treatment groups (ie, the intention-to-treat group and the completed therapy group) were comparable in terms of mean age (p=0.616 vs 0.406), sex distribution (p=0.78 vs 0.414), height (p=0.071 vs 0.09), pretreatment white blood cell counts (p=0.843 vs 0.549), prior antibiotic use (p=1.000 vs 0.732), diabetes mellitus (p=0.548 vs 0.508), infection (p=0.306 vs 0.415), and positive blood cultures (p=0.266 vs 0.474). However, the mean weight in the cefepime group was significantly less than that of the ceftazidime group in both the intention-to-treat and completed therapy groups (p=0.008 and 0.006, respectively). Of the 42 evaluable patients, 36 (86%) had UTI (21 in the cefepime group and 15 in the ceftazidime group), and one of them had concomitant pneumonia. The remaining 4 patients had biliary tract infections (BTI) (1 in the cefepime group and 3 in the ceftazidime group). One patient had salmonellosis and one had pneumonia. Cultures of the blood obtained at entry into the study were positive in 19 (45%) of the evaluable cases.

No significant difference in the total number of microbiologically documented infections was found between the treatment groups (Table 2). Infections were microbiologically documented in 41 (98%) patients (24 in the cefepime group and 17 in the ceftazidime group). Among these patients, 6 (14%) had polymicrobial infections; 4 (17%) in the cefepime group and 2 (11%) in the ceftazidime group. Polymicrobial infections were more frequent in the cefepime group, although this difference was not significant. *E. coli* was the most commonly isolated microorganism in both patient groups (33 isolates, 79%), followed by *K. pneumoniae* (6 isolates, 14%). Nineteen (45%) patients had either one or more positive pretreatment blood cultures; 12 (50%) in the cefepime group and 7 (39%) in the ceftazidime group. A total of 72 pathogens were isolated from different clinical specimens before treatment was initiated (40 from the cefepime group and 32 from the ceftazidime group). Of the 60 isolates tested for susceptibility to cefepime and ceftazidime, all but one strain of *Enterococcus* were susceptible to both drugs.

Table 3 shows the results on clinical and bacteriologic response. Of the 24 evaluable patients randomized to receive cefepime, 17 (71%) were clinically cured and 21 (87.5%) achieved bacteriologic eradication. The clinical outcome was failure or unable to determine in 7 patients. Of the 6 patients with failure

Table 3. Clinical and bacteriologic response rates

	Cefepime n = 24 (%)	Ceftazidime n = 18 (%)	95% Confidence interval Cefepime-Ceftazidime
Clinical response			
Cure	17 (70.8)	11 (61.1)	(–19-39)
Non-cure[a]	7 (29.2)	7 (38.9)	
Failure	6 (25.0)	7 (38.9)	
Unable to determine	1 (4.2)	0	
Bacterial response			
Eradication	21 (87.5)	16 (88.9)	(–21%-18%)
Non-eradication[b]	3 (12.5)	2 (11.1)	
Persistent	3 (12.5)	1 (5.6)	
Unable to determine	0	1 (5.6)	

[a]Non-cure is "Failure" + "Unable to determine"
[b]Non-eradication is "Persistent" + "Unable to determine"

outcome, 3 had a relapse of *E. coli* UTI; 2 had UTIs with persistent pyuria, and one had fungal superinfection. Two patients died. A 78-year-old bedridden man with multiple medical problems including previous myocardial infarction and previous cerebral infarction died from superinfection with *Candida albicans* and *Candida tropicalis* in the lung and urinary tract while he was being treated for pneumonia and UTI with *K. pneumoniae* bacteremia. The other patient was a 78-year-old diabetic woman who unexpectedly experienced hypercalcemia and disturbed consciousness on the 12th day of therapy for *E. coli* urosepticemia. Her condition deteriorated and she died on the 26th day of admission. Her death was suspected to be due to complications of paraneoplastic syndrome of occult malignancy. Elevated squamous-cell-carcinoma associated antigen, CA-125, and chorioembryoic antigen were found, but no autopsy was done. All 3 patients with persistent bacteriologic infection or relapse of *E. coli* UTI had diabetes mellitus.

Of the 18 evaluable patients randomized to receive ceftazidime, 11 (61%) were clinically cured and 16 (89%) had bacteriologic evidence of eradication after treatment. There was no significant difference between the 2 treatment groups. The clinical status was worsened after therapy in 7 patients: one with *Enterococcus* superinfection, one with *K. pneumoniae* and *E. coli* superinfection, 4 with UTI and persistent pyuria, and one with relapse of BTI for whom bacteriologic data was unavailable. Three of these 7 patients had diabetes mellitus and one had urinary bladder cancer who underwent operation several years ago. For those 2 patients whose bacteriologic response was not eradicated after therapy, one patient had persistent *E. coli* bacteriuria and another patient with BTI had no bacteria isolated from clinical specimens.

Both drugs were well tolerated, and the clinical safety was comparable in the 2 groups (Table 4). The most common adverse effects were hyperkalemia (12%), impaired liver biochemistry (12%), diarrhea (10%) and hypoalbuminemia (10%), which are commonly observed with the use of other cephalosporins. Five patients, 2 (8%) in cefepime group and 3 (12%) in ceftazidime group, reported local intolerance at the injection site, but all continued treatment. Other adverse events occurring during therapy included femoral neck fracture resulting from an accident of falling down from the bed in one patient in the cefepime group; upper airway viral infection syndrome in one patient in the cefepime group and one patient in the ceftazidime group; and disturbed consciousness as a complication of hypercalcemia in one patient in the cefepime group. Biologic tolerance of both treatments was good. The abnormal laboratory test results detected in 10 cefepime patients and 9 ceftazidime patients were not sufficiently severe to necessitate the discontinuation of treatment. Most of the abnormal results were transiently impaired liver biochemistry and hyperkalemia. Two patients treated with cefepime died, one from superinfection and one from suspected paraneoplastic syndrome. No early death was attributable to the study medication.

Discussion

Due to the development of bacterial resistance to existing antibiotics, the search continues for new drugs with an enhanced antibacterial spectrum and improved pharmacokinetic properties. Since the discovery of antibiotics, cephalosporins have attracted more attention than any other class of drugs. Cefepime is a methoxyimino-aminothiazolyl cephalosporin with a quaternized N-methyl-pyrrolidine moiety at the 3' position conferring zwitterionic properties [25]. It has superior antistaphylococcal and antipseudomonal

Table 4. Adverse events in 2 treatment groups

Adverse effect	Cefepime n = 26 (%)	Ceftazidime n = 26 (%)	p^a
Hyperkalemia	5 (19.2)	1 (3.8)	0.19
Impaired liver biochemistry	5 (19.2)	1 (3.8)	0.19
Diarrhea	3 (11.5)	2 (7.7)	1.00
Hypoalbuminemia	2 (7.7)	3 (11.5)	1.00
Local intolerance at injection site (including phlebitis)	2 (7.7)	3 (11.5)	1.00
Anemia	1 (3.8)	3 (11.5)	0.61
Impaired renal function	2 (7.7)	1 (3.8)	1.00
Leukopenia	1 (3.8)	2 (7.7)	1.00
Upper airway viral infection syndrome	1 (3.8)	1 (3.8)	
GI upset	1 (3.8)	0	
Insomnia	1 (3.8)	0	
Skin itch/rash	1 (3.8)	0	
Headache	1 (3.8)	0	
Disturbed consciousness	1 (3.8)	0	
Femoral neck fracture	1 (3.8)	0	
Dizziness	1 (3.8)	0	
Hypercalcemia	1 (3.8)	0	
Gouty arthritis	0	1 (3.8)	
Acute urine retention	0	1 (3.8)	

[a]Fisher's exact test

activities compared with third-generation cephalosporins and is more stable to hydrolysis by β-lactamases. *In vitro* studies of cefepime have shown good activity against many gram-positive and gram-negative organisms, including *Streptococcus pneumoniae*, α-hemolytic streptococci, methicillin-susceptible *Staphylococcus aureus*, coagulase-negative *Staphylococcus* species, the majority of *Enterobacteriaceae*, and *Pseudomonas* [26-29]. In view of its broad spectrum of activity, cefepime is an excellent choice for initial therapy in patients with severe bacterial infections. Initial trials with cefepime conducted in patients with community-acquired infections showed excellent activity for the most common indications [30]. Later in its development, cefepime was evaluated in the treatment of more severe infections as well as in nosocomial infections [31-35], the primary indication for this fourth-generation cephalosporin, and showed a satisfactory response. The clinical and microbiologic cure rates of cefepime reported in those studies were 79% to 98% and 85% to 95%, respectively, which was comparable to the rates for ceftazidime, 79% to 88% and 76% to 96%, respectively [5,20,30-32]. Studies with other cephalosporins or carbapenems showed comparable clinical (88%-100%) and microbiologic (79%-95%) response rates [1,2,36-38]. This study was specifically designed to evaluate cefepime in the treatment of severe bacterial infections with sepsis syndrome and to compare its efficacy with that of ceftazidime. This open, randomized study compared the safety and efficacy of intravenous cefepime, 2 g every 12 h with that of the intravenous ceftazidime, 2 g every 8 h, as empirical therapy for non-neutropenic adult patients with serious infections of demonstrated or suspected bacterial etiology. The treatment groups had similar demographic characteristics except for the body weight which was significantly higher in the ceftazidime group. In the analysis of evaluable cases, no significant differences were found in the clinical and bacteriologic response rates between patients treated with cefepime and ceftazidime. Although the clinical cure rate with cefepime (71%) was higher than that of ceftazidime (61%), this difference was not significant (95% CI: −19%-39%; p=0.53, Fisher's exact test). The results of this study suggest that monotherapy with cefepime is at least as efficacious as monotherapy with ceftazidime for the treatment of hospitalized patients with severe infection. The bacteriologic eradication rates of cefepime and ceftazidime groups were similar and were comparable to previous studies.

In this study, 24 (46%) patients had positive blood cultures; which is higher than the predictive value of bacteremia (24%) in patients fulfilling the diagnosis of SIRS [39], but comparable to that (47%) of a larger series [32]. This high percentage of positive blood cultures may have been due to the inclusion of patients with a clinically detected or suspected focus of infection in this study. The majority of the pathogenic isolates in

the studied patients were *E. coli*, (65% of the 52 patients, 58% of the 24 bacteremic patients) and most of them were found in blood or urine from patients with UTI. These findings are consistent with epidemiologic observations that *E. coli* is the most common gram-negative pathogen isolated from the bloodstream of hospitalized patients [40]. Notably, one patient with *S. paratyphi* A septicemia was cured after 2 weeks of cefepime treatment which has not been previously reported. Another patient with salmonellosis, presenting with UTI, pneumonia, infective spondylitis, and bacteremia, had a good response to cefepime therapy.

Cefepime has an excellent safety profile in the treatment of lower respiratory tract infections, UTIs, and skin or soft tissue infections [5,20,41]. Adverse effects associated with cefepime occurred in only 13. 8% of patients, which is comparable to the rate for ceftazidime, 15.6% [20]. In the present study, the most common adverse effects of cefepime were headache (2. 4%), nausea (1.8%), rash (1.8%), and diarrhea (1.7%). In this study, the overall safety profile of cefepime was excellent and comparable to that of ceftazidime. The adverse events reported included hyperkalemia, impaired liver biochemistry, hypo-albuminemia, and diarrhea, which are commonly observed with other cephalosporins. All of these adverse events or abnormal laboratory values returned to normal levels after treatment was completed or discontinued. However, 5 (10%) patients reported local intolerance at the injection site. This high incidence of phlebitis was probably due to a higher detection rate from a thorough daily inspection of the intravenous access sites and due to the relatively high doses of antibiotics that were given. None of the patients in either group required discontinuation of the drug or dose reduction due to adverse events. These findings indicate that cefepime 2 g every 12 h or ceftazidime 2 g every 8 h are safe for the treatment of severe infections in hospitalized patients.

Selecting appropriate empirical therapy for patients with suspected gram-negative bacteremia can be difficult. The spectrum of activity of cefepime includes *S. pneumoniae*, *Haemophilus influenzae*, *Enterobacteriaceae*, *Pseudomonas* spp., and methicillin-susceptible staphylococci. The activity of cefepime has been shown to be comparable to that of ceftazidime in various gram-negative infections [11,12]. Ceftazidime has been shown to be efficacious as empirical therapy for bacteremia, even in neutropenic hosts [3]. The present results suggest that cefepime is as efficacious and well tolerated as ceftazidime in the initial treatment of severe bacterial infections including septicemia, UTI, bacterial bronchitis, bacterial pneumonia, and intraabdominal infection. Further studies of cefepime are required to confirm that cefepime is an effective therapeutic option for the treatment of serious bacterial infections.

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