Efficacy and Safety of Twice Daily Administration of Cefpirome in the Empiric Treatment of Sepsis

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Abstract

Cefpirome is a fourth-generation cephalosporin with good activity against both gram-positive and gram-negative bacteria. A multicentre trial was performed to study the efficacy and safety of cefpirome 2 g twice daily in the treatment of sepsis. Sixty-three cases were recruited from 10 hospitals from April 1996 to January 1998. Fifty seven cases could be evaluated according to the protocol. The APACHE II score was used to measure severity of illness, with 46.9 per cent of patients having APACHE II score more than 10 and two patients more than 20; both were cured. The most common pathogens were gram-negative bacteria with *E. coli* predominating 16/40 (40.0%), followed by *Klebsiella* 8/40 (20.0%). The overall clinical success rates were 54 out of 57 patients (94.7%). In patients with positive blood culture, the clinical cures were achieved for 20/22 (90.9%). Cefpirome showed good efficacy and safety in the empirical treatment of suspected bacteremia or sepsis.

Key word : Cefpirome, Sepsis, Efficacy, Safety

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Cefpirome is a fourth-generation cephalosporin which bears a 2, 3-cyclopentenopyridium at the C-3 position of the cephem nucleus. It belongs to the parenteral 2-amino-5-thiazolyl cephalosporins[1]. Cefpirome displays a broad antibacterial spectrum including difficult-to-treat gram negative bacilli, such as members of *Enterobacteriaceae* producing class I ß-lactamase. This property is partly due to the zwitterionic structure of the compound, which allows for rapid penetration through the outer membrane of gram-negative bacilli and a high affinity for penicillin-binding proteins[2-5]. Cefpirome is active against numerous clinically significant gram-positive and gram-negative bacteria, including both aerobes and anaerobes[6-8].

Cefpirome is rapidly and widely distributed in body fluids with high tissue penetration, reaching concentrations which exceed the minimum inhibitory concentrations for most pathogens[9]. The drug is approved for the management of lower respiratory tract infections, septicemia, skin and soft tissue infections, complicated upper and lower urinary tract infections, infections in neutropenic patients and in severe infections in intensive care patients. It can also be considered for the empiric treatment of bacterial infections, such as septicemia, when the causative pathogen has not yet been identified and rapid initiation of an effective antibiotic regimen is mandatory.

The safety profile of cefpirome is similar to other parenteral broad spectrum cephalosporins with low serum protein binding.

We investigated the efficacy and safety of cefpirome 2.0 g twice daily in the treatment of sepsis in a multicenter study including 10 hospitals in Bangkok and upcountry.

MATERIAL AND METHOD

Sixty three hospitalized patients with clinical signs and symptoms suggesting septicemia were recruited from 10 hospitals in Bangkok and upcountry areas from April 1996 to January 1998. The patients were between 18-80 years and had clinical evidence of bacterial infection i.e. respiratory tract infection, urinary tract infection, etc. plus two or more of the following criteria : temperature > 38°C or < 36°C, heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute or P_aCO_2 < 32 mmHg, WBC > 12/nl or < 4/nl or > 10 per cent band forms.

Patients were excluded from participation in the study if they had a history of hypersensitivity to cephalosporins or a documented history of type I hypersensitivity to penicillin, and indication for antibiotic treatment other than the study medication, refractory septic shock, critically ill patients with multiorgan failure, progressive fatal disease, chronic renal failure, HIV positive, or mental condition. Pregnant women, women who were breastfeeding and in whom pregnancy was possible were not enrolled.

Patients were withdrawn if the clinical response was unsatisfactory (even though *in vitro* testing may indicate that the initial causative pathogen is sensitive to cefpirome or no pathogen(s) have been found in the pretreatment culture). Other reasons for withdrawal included resistant pathogen in pretreatment culture unless clear clinical improvement was decided by investigator to warrant continuation of cefpirome, and serious or alarming adverse drug reactions related to cefpirome.

During the 24 hours before study entry all patients underwent a physical examination. Age, sex, weight, height and vital signs, neurological abnormalities, infection-related symptoms indicating septicemia and the site of infection were documented. Chest X-ray was done in patients with suspected respiratory tract infection and cultures were obtained from the appropriate sites. Hematological and biochemical parameters were determined in all cases and blood was taken for cultures before, during and after treatment. Two grams of cefpirome was injected intravenously twice a day. The duration of treatment depended on the clinical response.

The final evaluation including assessment of the clinical and bacteriological response was done at the end of the treatment and 14 days after.

Clinical response was defined as: cure, improvement or failure (infection-related symptoms remained unchanged or worsened).

Bacteriological response was defined as satisfactory (eradication or presumed eradication), unsatisfactory (persistence of causative organism or a new or additional antimicrobial therapy was required because of clinically persisting infection at the original site in the absence of microbiological data relapse, reinfection) and undetermined (no possibility to categorize the bacteriological response because of any reasons).

All adverse events observed by the investigator or reported by the patient were documented.

RESULTS

A total of 63 cases were recruited from the 10 centers from April 1996 to January 1998. Fifty seven cases could be evaluated according to the protocol. Reasons for excluding 6 cases were protocol violation.

There were more female patients (66.7%) and the average age was 52.6 years. The Apache II score average was 10.8 ± 4.9 indicating the severity of sepsis with 46.9 per cent having an Apache II score more than 10 and two patients more than 20. Both of the 2 most severe patients were cured. Sixty three percent of patients had underlying diseases among which diabetes was the most common (19%) (Table 1).

The most common pathogens were gram-negative bacteria with *E. coli* predominating 16/40 (40.0%), followed by *Klebsiella* 8/40 (20.0%). Thirty six out of 40 (90.0%) patients had satisfactory bacteriological response (Table 2).

Table 3 shows clinical response at the end of treatment day; twenty two out of 57 patients (38.6%) had positive blood culture either with or without focal infections. In patients with positive blood culture, 90.9 per cent were considered cured. In patients with negative blood culture, 97.1 per cent were considered cured. Of the forty patients who came for follow-up on the 14th day post-treatment, all were cured. There was no relapse or reinfection.

Adverse events reported in 9 patients including drug fever, rash (2 patients each), eosinophilia and thrombocytosis (1 patient each). Two patients had mild elevation of serum creatinine, the significance of which is unknown.

DISCUSSION

Mortality resulting from septicemia appears to be multifactorial and dependent on geographic distribution of the causative pathogen, underlying

Table 1. Patient characteristics (n = 63).

Characteristics	No. of patients	Percentage
Sex		
Male	21	33.3%
Female	42	66.7%
Age (years)		
Mean ± SD	52.6 ± 15.9	
Range	17 - 80	
APACHE II Score		
≤ 10	26	53.1%
11 - 20	21	42.8%
> 20	2*	4.1%
Mean ± SD	10.8 ± 4.9	
Range	3 - 26	
Patient with underlying diseases**	40	63.5%
- Diabetes mellitus	12	19.0%
- Hypertension	8	12.7%
- Renal disease	7	11.1%
- Chronic liver disease	6	9.5%
- Alcohol abuse	5	7.9%
- Malignancy (solid tumors)	5	7.9%
- Cardiovascular disease	5	7.9%
- Gastrointestinal disease	3	4.8%
- COPD/Asthma	3	4.8%
- Epilepsy	2	3.2%
- Other	5	7.9%

* The 2 patients with APACHE II Score 26 and 21 were cured.
** One patient may have more than one underlying diseases.

Table 2. Bacteriological results (Per Protocol Analysis).

Organism	Outcome		
	Satisfactory	Unsatisfactory	Undetermined
Gram negative			
Acinetobacter spp.	1	1	-
E.coli	16	-	-
Enterobacter cloacae	2	-	-
Enterobacter species	1	-	-
Klebsiella pneumoniae	4	-	1
Klebsiella species	4	-	-
Proteus mirabillis	1	-	-
Pseudomonas aeruginosa	2	1	-
Gram Positive			
Staphylococcus aureus	3	-	-
Staphylococcus epidermidis	1	-	-
Strep. pneumoniae	1	-	-
ß-hemolytic strep. not gr. A&D	-	-	1
Total	36 (90.0%)	2 (5.0%)	2 (5.0%)

Table 3. Clinical response (Per Protocol Analysis).

Type of infection	Clinical response at end of cefpirome treatment	
	Cure	Failure
Sepsis with positive blood culture (n=22)	20 (90.9%)	2 (9.1%)
1. without focal infection (n = 11)	9	2
2. with focal infection (n =11)	11	0
2.1 Upper UTI	8	-
2.2 Cellulitis	1	-
2.3 Intraabdominal infection	1	-
2.4 Empyema & Infected cutdown wound	1	-
Sepsis with negative blood culture (n=35)	34 (97.1%)	1 (2.9%)
1. without focal infection (n = 3)	3	-
2. with focal infection (n = 32)	31	1
2.1 Pneumonia/RTI	6	-
2.2 Upper UTI	14	-
2.3 Cellulitis	3	1
2.4 Intraabdominal infection	5	-
2.5 Retroperitoneal abscess	1	-
2.6 Pneumonia and Upper UTI	1	-
2.7 Pneumonia and Cellulitis	1	-
Total	54 (94.7%)	3 (5.3%)

diseases, severity of illness and immune status of patients[10,11]. These factors can have a significant impact on treatment options particularly when considering initial or empiric antimicrobial therapy. Consequently, empiric treatment for assumed septicemia should be broad spectrum to cover the most likely causative organisms.

Changes in the epidemiology of infectious organisms and the growing emergence of multi drug-resistant bacteria make it necessary to continually reevaluate the therapeutic options. Fortunately, the number of therapeutic options has also been broadening as new antibiotics are introduced, including fourth-generation cephalosporins. Optimal and

cost-effective empiric therapy is directed by the findings of a clinical evaluation of the patient as well as an awareness of institutional patterns of infection and susceptibility of likely infecting organisms.

This multicentre study included quite a large number of moderately ill patients, as evidenced by relatively high APACHE II scores. The results of this study clearly show and suggest that cefpirome, a fourth generation cephalosporin, represents an effective empirical antibiotic regimen for both gram positive and gram negative bacterial sepsis, including multi drug-resistant organisms. This empiric regimen also demonstrated efficacy even in severe sepsis with very high APACHE II score as shown in 2 of our patients.

In conclusion this multicenter study indicates that a twice daily dosage of cefpirome is effective and well tolerated. Thus, cefpirome should be considered a valuable addition to the antibiotic armoury for the empiric regimen in moderate to severe infections[12-14].

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ประสิทธิภาพและความปลอดภัยของเซฟพิโรมในการรักษาภาวะติดเชื้อเซฟสิส

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เซฟพิโรมเป็นยากลุ่มเซฟาโลสปอริน รุ่นที่ 4 ซึ่งมีฤทธิ์ต่อต้านแบคทีเรียทั้งกรัมบวกและกรัมลบ การวิจัยทางคลินิกครั้งนี้ทำเพื่อศึกษาประสิทธิภาพและความปลอดภัยของการใช้เซฟพิโรม ขนาด 2 กรัม วันละ 2 ครั้ง ในการรักษาการติดเชื้อเซฟสิส ระหว่างเดือนเมษายน 2539 ถึงมกราคม 2541 ผู้ป่วย 63 รายจากโรงพยาบาล 10 แห่ง ได้รับการรักษาด้วยเซฟพิโรม ซึ่งมีจำนวน 57 ที่สามารถประเมินได้ตามโปรโตคอล ผู้ป่วย 46.9% มีคะแนน APACHE II ซึ่งแสดงความรุนแรงของโรคสูงกว่า 10 และมี 2 รายที่คะแนนสูงกว่า 20 ทั้ง 2 รายนี้รักษาหายด้วยเซฟพิโรม เชื้อที่เป็นสาเหตุที่พบบ่อยคือ เชื้อกรัมลบ ประกอบด้วย *E. coli* 16/40 (40.0%), *Klebsiella* 8/40 (20.0%) การรักษาได้ผลดีทางคลินิกใน 54/57 (94.7%) ของผู้ป่วย ในผู้ป่วยที่มีเชื้อแบคทีเรียเพาะขึ้นจากโลหิต อัตราการรักษาหาย 20/22 (90.9%) การศึกษานี้แสดงว่า เซฟพิโรมมีประสิทธิภาพและความปลอดภัยดี และสามารถใช้รักษาการติดเชื้อทั้งที่เพาะเชื้อขึ้นและไม่ขึ้นในโลหิต

คำสำคัญ : เซฟพิโรม, เซ็พสิส, ประสิทธิภาพ, ความปลอดภัย

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