

Safety and Efficacy of Cefpirome Among Filipino Patients

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Abstract

Background: Infectious diseases remain a significant cause of morbidity and mortality. Cefpirome, a fourth generation Cephalosporin, is a potent antibiotic against a wide variety of organisms that may be used alone or in combination with other antimicrobials to combat various infections.

Objective: This is a post-marketing surveillance study documenting the safety and efficacy of cefpirome among Filipino patients.

Methodology: This was a multicenter, open-label, non-comparative study involving 402 patients who received at least one dose of cefpirome. Safety and efficacy data were gathered.

Results: Cefpirome was used as monotherapy in majority of the cases. Pneumonia (76%) was the most frequent indication for the use of this drug. The most commonly utilized dosage regimen was 2.0 grams every 12 hours for a mean of 4.2 days. This was associated with a successful clinical outcome in almost 90% of cases. There was almost negligible side effect reported.

Conclusion: The use of cefpirome was shown to be safe and well-tolerated with associated successful clinical outcomes among Filipino patients.

Keywords: cefpirome, efficacy, Filipino

Introduction

Infectious diseases continue to cause significant adverse effects to the health of individuals and pose danger to communities. Their impact remains substantial despite the introduction of newer tools in the fields of diagnosis and treatment. This is especially true in cases of severe sepsis, nosocomial infections, and severe pneumonia.¹⁻³ Pneumonia continues to be among the top causes of morbidity and mortality. The current situation becomes worse when the afflicted individual becomes critically ill and possible resistant organisms emerge.

Antibiotics remain an integral part in the management of various infections. Their timely administration is proven to be an effective intervention that is consistently associated with favourable outcomes.⁴ Definitely, not only are effective antibiotics needed but there should also be rational use of currently available antimicrobial agents.^{1,4} A lot of antimicrobial classes are presently available in the country. Some classes are used more frequently because of their broad indication. Such practice needs to be monitored in order to ensure that the potency of these particular drugs will not be lost and the emergence of resistant strains can be prevented. Proper usage in terms of correct dose, frequency,

and duration given with the right indication has been proven to be associated with good outcomes.⁴

Cefpirome is a fourth-generation cephalosporin with good penetrating abilities against various microorganisms because of its unique structure.³ The molecule is basically an aminothiazolemethoxyimine with positive and negative charged ions embedded in focal positions that confer it with zwitterions properties. This feature allows a favorable antimicrobial attribute with a wide range of bactericidal activity against Gram positive and Gram negative microorganisms better than a third-generation cephalosporin. In addition, in-vitro studies demonstrate a lesser tendency in promoting resistance and stability against various beta-lactamases.⁵ These attributes make it a rational choice, used either alone or in combination, against a wide variety of infections.³⁻⁷

Initial laboratory investigations have likewise shown that cefpirome is active against a wide array of bacterial pathogens encountered in cases of urinary and lower respiratory tract infections, sepsis, bacteremia, febrile neutropenia, and infections in the intensive care units and skin and soft tissue structures.⁴ Clinical data further reinforce these findings with acceptable clinical experience on the use of cefpirome that was used as monotherapy or in combination with the appropriate antibiotics based on guidelines or clinical indication.^{1-2,7}

This post-marketing surveillance study was principally undertaken in order to document the clinical experience on the use of cefpirome among Filipino

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patients. Safety and efficacy endpoints were primarily monitored and documented.

Materials and Methods

Study Design

Multicenter, open-label, non-comparative study involving the use of cefpirome (Cefrin®, DexaMedica), a fourth-generation cephalosporin.

Inclusion Criteria:

1. Adult (at least 18 years old) Filipino patients
2. With moderate to severe infections primarily involving the respiratory and urinary tract, and skin and soft tissue structures. Patients could have also initially presented with bacteremia or sepsis with the source of infection still to be determined on admission.

Exclusion Criteria:

1. Female patients of childbearing potential
2. Individuals with known or suspected allergy to cefpirome, other cephalosporin, or β -lactam antibiotics.
3. Severely immunocompromised patients (patients with HIV/AIDS, cancer)- either documented or suspected by the attending physician that may warrant the use of other antibiotic regimen based on accepted standards of care.

Drug Preparation^{2,3}

Cefpirome sulphate is available as a 1.0 gram sterile powder for reconstitution in vials, administered as intravenous injection. The contents of one vial of 1.0 gram cefpirome was dissolved in 10ml sterile water for injection, and then administered over three to five minutes either directly into a vein or into the distal section of a clamped-off infusion tube. The following infusion solutions may also be used: 0.9% Sodium Chloride solution, Ringer's solution, standard electrolyte infusion, 5.0 and 10% glucose solution, 5% fructose solution, 6% glucose + 0.9% sodium chloride solution. Patients with normal renal function may be given a total daily dose of 2.0 or 4.0 grams depending on the severity of infection at the time of presentation. For patients with renal impairment, 0.25 or 0.5g of the contents were dissolved in 2.0 or 5.0 ml for injection, respectively. The dosage to be used, duration of treatment and mode of administration will be dependent on the clinician's judgment.

Data Collection

The study was conducted over approximately three years (2012-2014) in 24 tertiary hospitals. Informed consent was obtained from each individual or their

decision maker prior to administration of the first dose of cefpirome. Participants may withdraw from the study at any point for any reason or upon their clinician's prerogative. Cefpirome was used alone or in combination with other appropriate antibiotics based on the primary clinician's judgment and discretion.

Details of concomitant illness and medication were all recorded at study entry. All other procedures that were necessary in the management of the subject's infection were performed in compliance with accepted standards of care. Therefore, no concomitant therapies were restricted as long as they were deemed part of the management plan for the participants. All adverse events whether observed by the investigator or voluntarily reported by the patients were recorded at each visit and were classified according to their severity and possible casual relationship to the study treatment. Death and other serious adverse events were also monitored and documented. All patients who received at least one dose of cefpirome were evaluable for the final analysis. Each adverse event was followed up and appropriately addressed until an outcome could be assigned.

Endpoints

The efficacy endpoints included clinical response within 48 hours after initiating therapy as well as at the end of treatment with the study drug. Clinical response was categorized as to the following:

Success: Improvement or recovery of the patient's condition based on the physician's clinical judgment without modification of the initial therapy

Failure: The presence of at least one of the following-persistence or progression of disease symptoms: invasive superinfection, death due to infection, other conditions that necessitated modification or change of the antibiotic regimen.

Indeterminate: Condition cannot be adequately assessed.

Descriptive analysis was applied in both the safety and efficacy parameters.

Results

A total of 454 accomplished forms were initially submitted for analysis. Out of this, 52 had either incomplete entries or with unresolved queries. A total of 402 forms representing the same number of individual patients were available for the final analysis.

Male (n=213) and female (n=189) patients were almost equally represented in the study with a mean age of 61.9 years (range:30-82 years old). High risk community-acquired pneumonia was the main indication for starting antibiotics in the majority of cases (76.37%) and an infectious cause for the exacerbation of chronic obstructive pulmonary disease

(COPD) as the second most common indication (16.67%). Almost 3.5% of patients initially presented with severe sepsis or septic shock. A concomitant malignancy or hypertension was the most common co-morbidity identified among the included patients.

Table I: Demographics of study participants

PARAMETER	VALUE
Sex (M:F)	1.12:1
Age (mean and range in years)	61.9 (30-82 years old)
Concomitant illness:	
-Malignancy	22 (5.5%)
-Hypertension	16 (4%)
-Ischemic Heart Disease	12 (3%)
Indication for antibiotic:	
-Community acquired pneumonia	301 (75.37%)
-COPD in exacerbation	62 (15.67%)
-Nosocomial Pneumonia	20 (4.83%)
-Bronchiectasis	10 (2.43%)
-Complicated UTI	9 (2.20%)

Table II: Antibiotic usage

PARAMETER	DESCRIPTION
Cefpirome Dosage	
-Total Daily Dosage	4.0 grams (2.0 grams every 12 hours) in 94.3%
-Duration (mean number of days)	4.2 +/- 1.2 days
Cefpirome use	
-monotherapy	-61.94%
-in combination with other antibiotics	-38.05%
Efficacy Assessment	
-success at 48 hours	-85.6%
-success at end of study	-89.1%
Safety Assessment	
-No adverse event reported	-98.26%

In about two-thirds of cases, cefpirome was used alone. Majority of the participants (94.3%) received a total daily dosage of 4.0 grams cefpirome (2.0 grams every 12 hours) during the study period. When this agent was used in combination with other antibiotics, azithromycin was the most utilized followed by levofloxacin. The mean treatment duration with cefpirome was 4.2 days. There was no instance when the initiated dose was changed during the patient's hospital stay.

In terms of safety and tolerability, there was no adverse event reported or observed in 98% of patients. In the remaining number, only mild reactions were observed with rashes as the most commonly reported. In these instances, such reactions resolved after discontinuation of the drug. One patient died within 24 hours of admission to the hospital and

he received a single dose of cefpirome.

Overall, within 48 hours of antibiotic administration, 85.6% of cases were associated with a successful clinical outcome. Positive outcomes were likewise ascertained in 89.1% of cases by the end of study period.

Discussion

This post-marketing surveillance study revealed favorable outcomes on the use of cefpirome among admitted Filipino patients. Almost 90% of patients were evaluated to have a successful clinical outcome at the end of study period with adverse events reported to be very minimal. These results were consistent with the findings of similar studies.^{2,3,7} Cefpirome was shown both by clinical and in vitro studies to be active against a wide array of microorganisms principally implicated in sepsis, pneumonia, urinary tract infections, and infections affecting the skin and soft tissue structures.

Majority of the cases who were included suffered from infections of the respiratory tract. Lindenmann and colleagues had demonstrated the property of this antibiotic to effectively penetrate into the extracellular fluid of the lung tissue and achieving good levels in this compartment using microdialysis probes.⁵ This attribute makes it a rational choice for patients especially suffering from pneumonia requiring hospitalization and even critical care services. In our study, in around 38% of cases, a combination with azithromycin or levofloxacin was the most common regimen utilized. Such an action is consistent with the recommendations on the use of combination antibiotic therapy for severe pneumonia and those with respiratory or hemodynamic instability.^{1,8} This population is frequently infected with a polymicrobial nature and *Streptococcus Pneumoniae*, *Klebsiella spp.*, *Enterobacter spp.*, and other Gram negative organisms are often isolated in culture studies.

Similar organisms were likewise implicated in nosocomial pneumonia and bacterial exacerbations of chronic bronchitis and bronchiectasis.^{9,10} In these situations, guidelines always stress the importance of appropriate risk stratification and clinically profiling these individuals which will guide the physician in terms of logical initial choice of antibiotics. These should be administered without significant delays in order to have favorable impact on outcomes. The use of agents with anti-Pseudomonal properties is preferred especially among those with suitable risk factors, significant co-morbidities, and lung impairment.^{8,9}

Majority of patients in this study received a total daily dose of 4.0 grams cefpirome given at 2.0 grams every 12 hours, with a mean duration of around four days. Cefpirome's serum half-life of around two hours,

together with its good tissue penetration, allows for this twice-a-day regimen. Some were able to switch to an oral agent by the second to the third day of antibiotic administration. This observed trend can potentially translate to cost-savings. A similar strategy was employed among febrile neutropenic patients.³ In this study, a four gram daily dose was associated with an 88.6% clinical improvement with a mean time to fever resolution of 3.1 days.

The optimal method of administering beta-lactam antibiotics, like cefpirome, in septic and critically-ill patients has been a subject of recent studies.¹¹⁻¹⁵ This particular group of patients may require certain maneuvers to ensure optimal antibiotic efficacy. This unique scenario may be due to a lot of factors like reduction in protein binding, low albumin states, variations in volume of distribution, possible enhanced antibiotic clearance due to a hyperdynamic state which may be contributed by the use of vasopressors and fluid resuscitation, and presence of co-morbidities requiring certain concomitant treatment.^{12-13,15} Antibiotic underdosage may be a critical issue and may be associated with poor clinical outcomes and possible emergence of resistance. It is the general recommendation that in order for this class of antimicrobials to effectively kill bacteria, the free drug concentrations (f) should be above a minimum inhibitory concentration (MIC).¹⁵ Laboratory studies have shown that this particular proportion (fT> MIC) should be about 60-70% to accomplish near-maximal bacterial killing. This translates to a required dose of around 40-60% of the dosing interval and probably around 70% for more virulent organisms like *Pseudomonas*.^{12,15}

Cefpirome has been shown to achieve levels in subcutaneous adipose and extracellular lung tissues greater than MIC's of most bacteria isolated among septic patients.^{5,14} However, effective levels were difficult to achieve and sustain with the usual dose of 2.0 grams every 12 hours when difficult-to-treat organisms like *Pseudomonas aeruginosa* and *Acinetobacter* spp. were used in pharmacokinetic modeling studies.^{12,14,15} Interindividual variability was likewise demonstrated among infected individuals, making the proper dosing in this situation quite challenging.¹⁴ For these particular Gram-negative bacteria, the following maneuvers may be resorted to: a higher total daily dosage, possibly at 2.0 grams every eight hours, may be given¹⁴, a continuous infusion of 4.0-6.0 grams may be administered daily¹², or more frequent dosing at 1.0 gram every four hours (total daily dose of 6.0 grams) may be employed.¹² These actions take advantage of the features of a time-dependent antibiotic and maintain the plasma concentration above a critical level while minimizing the fluctuations. Studies that examine the association of such administration techniques and outcome are

needed in order to further prove the benefits of the lessons that these models provide.

Almost all included patients in our study did not experience adverse events. Overall, one patient who received a single dose of cefpirome died within 24 hours of admission. This individual presented with septic shock at the emergency room and this fatal outcome was judged to be more secondary to the severity and course of his illness. In general, low side effects are observed with the use of beta-lactam antibiotics. A similar favorable safety profile was seen in previous clinical investigations.^{2,3,7} Cefpirome was well-tolerated as a monotherapy or when used in combination with other antimicrobials.

Conclusion

This post-marketing surveillance study on the use of cefpirome among Filipino patients has shown that this antibiotic was generally safe and well-tolerated. In addition, the commonly used dose of 2.0 grams every 12 hours was associated with favorable outcomes with almost 90% assessed to have clinical improvement by end of study period.

References

1. **Caballero J, Rello J.** Combination Antibiotic therapy for Community-Acquired Pneumonia. *Annals of Intensive Care*.1:48-53, 2011.
2. **Wolff M. et al.** Comparison of strategies using Cefpirome and Ceftazidime for empiric treatment of Pneumonia in intensive care units. *Antimicrobial Agents and Chemotherapy*. p28-36, 1998.
3. **Yu-Chieh Su et al.** An observational study on the empiric use of cefpirome in febrile neutropenia. *Journal of Microbiology, Immunology and Infection*. 40:62-67, 2007.
4. **Dellinger RP. et al.** Surviving Sepsis Campaign: International Guidelines for the Management of Severe Sepsis and Septic Shock: 2012. *Critical Care Medicine*.41(2): 580-637, 2013 February.
5. **Lindenmann J et al.** High extracellular levels of Cefpirome in unaffected and infected lung tissue of patients. *Journal of Antimicrobial Chemotherapy*. 66(1): 160-164, 2011.
6. **Jain A. Sing K.** Recent advances in the management of nosocomial infections. *Journal of Medical Education and Research*(JK Sciences). 9(1):3-8; 2007.
7. **Norby S. et al.** Randomized comparative trial of cefpirome versus ceftazidime in the empirical treatment of suspected bacteremia or sepsis. *Journal of Antimicrobial and Chemotherapy*. 42: 503-509, 1998.
8. **Philippine Clinical Practice Guidelines on the Diagnosis, Empiric Management and Prevention of Community Acquired Pneumonia in Immunocompetent Adults 2010 Update.**
9. **American Thoracic Society and Infectious Disease Society of America.** Guidelines for the management of Adults with Hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*. 171:388-416, 2005.
10. **King PT and Holmes PW.** Use of antibiotics in Bronchiectasis. *Reviews on Recent Clinical Trials*. 7(1): 24-30, 2012 February.

11. **Jacolot A. et al.** Pharmacokinetics of Cefpirome during the posttraumatic systemic inflammatory response syndrome. *Intensive Care Medicine.* 25:486-491, 1999
12. **Lipman J. et al.** Low cefpirome levels during twice daily dosing in critically ill septic patients: Pharmacokinetic modeling calls for more frequent dosing. *Intensive Care Medicine.* 27:363-370, 2001.
13. **Joukhadar C. et al.** Plasma and tissue pharmacokinetics of Cefpirome in patients with sepsis. *Critic Care Medicine.* 30(7): 1478-1482, 2002.
14. **Sauermann R. et al.** Pharmacokinetics and pharmacodynamics of cefpirome in subcutaneous adipose tissue of septic patients. *Antimicrobial Agents and Chemotherapy.* 49(2):650-655, 2005.
15. **Roos J. et al.** Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-Negative bacteria. *Intensive Care Medicine.* 33:781-788, 2007.