

In-Vitro Antimicrobial Activity of Cefpirome: a new fourth-generation Cephalosporin against clinically significant Bacteria

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Abstract

Objective: To study the in -vitro antimicrobial activity of Cefpirome : A new fourth generation Cephalosporin in comparison with other agents against clinically significant Gram-negative and Gram-positive bacteria.

Setting: A multi-center in-vitro study was conducted in 13 centers.

Materials and Methods: Bacterial isolates - A total of 1300 isolates were collected from different clinical laboratories and hospitals at 13 centers. Organisms were identified by the API identification systems (API systems, SA Vericeu, France). The age and sex of each patient, type of hospital unit, source of the isolate and genus and species of the bacteria were recorded on standardized report forms. The sensitivity testing was carried out by the NCCLS (modified Kirby-Bauer) method” - using Mueller-Hinton agar. Results: The results suggest that Cefpirome has a potential clinical advantage against gram-positive and gram-negative bacteria resistant to other third generation cephalosporins.

Conclusion: Cefpirome was active against both gram-negative and grain-positive organisms. Cefpirome was more active than ceftazidime, cefoperazone, ceftizoxime and ceftriaxone against E.coli, Klebsiella spp, Enterobacter spp, Proteus spp, Salmonella typhi, Enterococci, methicillin sensitive Staphylococci and Betahemolytic Streptococci. The activity of Cefpirome was comparable with ceftazidime against pseudomonas aeruginosa. Cefpirome had the smallest numbers of resistant isolates. Cefpirome was more active than other third generation cephalosporins compared in this study against E.coli (87% vs 61%), Klebsiella spp (84% vs 56%), Enterobacter spp (88% vs 59%), Proteus spp (97% vs 92%) , Salmonella typhi (98% vs 96%), methicillin sensitive Staphylococci (86% vs 59%) and Enterococci spp (82% vs 72%) (JPMA 50:250, 2000).

Introduction

Cefpirome is a fourth-generation cephalosporin¹ with a wide range of anti-bacterial activity². Cefpirome has a superior overall activity against gram-negative organisms compared to the best of the third-generation cephalosporins³. It is active against multi-resistant Enterobacter, Citrobacter, Kiebsiella and Escherichia strains. Cefpirome had demonstrated activity against Staphylococcus aureus, coagulase-negative Staphylococci and Enterococci many of which are relatively insensitive to the other third-generation cephalosporins^{4,7}. The excellent activity of Cefpirome, in-vitro and in animal models is borne out by extensive clinical support from a world-wide trials programe. The compound shared the favorable tolerability profile of other

penicillins and cephalosporins. It should be regarded as an important addition to the armamentarium available for the empirical treatment of life threatening infections.

Material and Methods

Bacterial isolates: A total of 1300 isolates were collected from different clinical laboratories and hospitals at 13 centers in Pakistan. Organisms were identified by the API identification systems (API systems, SA Vericeu, France) . The age and sex of each patient, type of hospital unit, source of the isolate and genus and species of the bacteria were recorded on standardized report forms.

Susceptibility Testing

Sensitivity testing was carried out by the “NCCLS (modified Kirby-Bauer) method”- using Mueller-Hinton agar⁸. The inoculum used was equivalent to 0.5 Barium sulphate standard. The diameters of the zones of inhibition are interpreted by referring to table, which represents the NCCLS sub-committee’s present recommendations. Reference strains *Escherichia coli* ATCC 25922, *Staphylococcus aureus*

ATCC 25923 and *Pseudomonas aeruginosa* ATCC 27853 were provided to each center. Each investigator tested these at intervals throughout the study for quality control purpose.

Results

The in-vitro antibacterial activities of Cefpirome and other antibiotics tested against 1300 isolates are presented in Tables 1,2 and 3.

Table 1. Comparison of activity of selected antibiotics against gram-negative bacteria.

Organism	No.	Cefpirome %sensitivity			Ceftazidime % sensitivity			Cefoperazone %sensitivity			Ceftizoxime %sensitivity			Ceftriaxone %sensitivity		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>E.coli</i>	255	87	5	8	69	7	24	52	14	34	62	12	27	62	13	26
<i>Enterobacter spp</i>	84	88	6	6	63	7	30	54	20	26	56	10	33	62	17	22
<i>Klebsiella spp</i>	182	84	12	10	56	7	37	52	20	28	68	15	23	49	24	26
<i>Proteus spp</i>	63	97	3	0	95	0	5	90	7	3	90	3	7	93	2	5
<i>S. typhi</i>	54	98	2	0	96	0	4	94	4	2	96	0	4	95	5	0

Table 2. Comparison of activity of selected antibiotics against gram-positive bacteria.

Organism	No.	Cefpirome %sensitivity			Ceftazidime % sensitivity			Cefoperazone %sensitivity			Ceftizoxime %sensitivity			Ceftriaxone %sensitivity		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>Staph. Aureus (MSSA)</i>	216	86	5	10	58	7	35	59	18	23	62	5	33	57	11	18
<i>B-hemolytic Streptococci</i>	9	100	0	0	100	0	0	100	0	0	100	0	0	100	0	0
<i>Enterococcus Spp*</i>	38	82	0	18	74	4	22	74	6	20	74	2	24	68	2	30

S = Sensitive; I = Intermediate; R = Resistant

Table 3. Comparison of activity of selected antibiotics against non-fermenters.

Organism	No.	Cefpirome %sensitivity			Ceftazidime % sensitivity			Cefoperazone %sensitivity			Ceftizoxime %sensitivity			Ceftriaxone %sensitivity		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
<i>Ps. aeruginosa</i>	174	74	11	15	80	7	13	60	15	25	16	12	72	32	23	45
<i>Acinetobacter Spp.</i>	79	42	14	43	34	11	55	16	7	78	17	9	74	9	9	82

Cefpirome was active against a broad range of organisms. Majority (68%) of the organisms were isolated from pus, urine and blood while 32% of the isolates were from other sources.

Cefpirome was more active against Enterobacteriaceae as compared to other third generation cephalosporins. In the group of non-fermenters, Cefpirome was more active than other 3rd generation cephalosporins against *Acinetobacter spp.* In case of *Ps. aeruginosa*, Cefpirome was more active than cefoperazone, ceftizoxime and ceftriaxone. However there was no statistically significant difference in the comparative activities of Cefpirome and ceftazidime against this problem pathogen (74% vs 80%). Cefpirome showed the highest activity against methicillin sensitive staphylococci and enterococci as compared to other third-generation cephalosporins used in this study.

Discussion

Antimicrobial resistance is a significant clinical problem when treating patients in the ICU⁹. This resistance is achieved usually through one or more of four ways; decreased antibiotic permeability through the cell wall; antibiotic inactivation; alteration of the target binding site & active antibiotic efflux. Without identifying the mechanism of resistance, it is impossible to determine precisely whether the cross-resistance to two agents is due to the same mechanism, therefore, labels of “cross-resistance” may be true but may be due to completely different molecular mechanisms. Organisms with plasmid-mediated, broad-spectrum Beta.lactamses such as *E.coli*, *Enterobacter spp* and *Kiebsiella spp* have been identified in both the ICU as well as in chronic care settings¹⁰⁻¹⁶.

Additionally, gram-negative organisms such as *Ps. aeruginosa*, *Enterobacter spp*, *Citrobacter spp* and *Serratia spp* have inducible chromosomally mediated Beta-lactamases capable of inactivating extended spectrum penicillins and third generation cephalosporins, agents very commonly used in the intensive care setting¹⁷.

Drug resistant bacteria contribute to increased patient morbidity and mortality, so new ways of encountering this resistance must continually be developed and exploited. Cefpirome is a fourth generation cephalosporin with superior activity against bacteria capable of producing an inducible Class 1 Beta-lactamases¹⁸, Constitutive hyper-producing isolates are often sensitive to Cefpirome while remaining resistant to other broad-spectrum antimicrobials^{19,5,6}. This activity was especially evident against *E. coli* (87%), *Enterobacter spp.* (88%), *Klebsiella spp.* (84%) and *Proteus spp.* (92%) tested in this study.

There was significant cross-resistance among the cephalosporins in this study with the exception of Cefpirome. It was much more active than the other cephalosporins against all single drug resistant bacteria. The total number of Cefpirome resistant isolates were fewer than the numbers seen with ceftazidime, ceftriaxone, cefoperazone and ceftizoxime. The relative lack of cross-resistance between Cefpirome and the third generation cephalosporins suggests a slightly different mechanism of action of Cefpirome in comparison to the other cephalosporins.

Cefpirome because of its compact dipolar structure penetrate gram-negative bacteria more

quickly than the other agents and as such can be bactericidal in a shorter time^{20,18}. The in-vitro results from the current study suggest that Cefpirome has a potential clinical advantage against gram-positive and gram-negative organisms resistant to other Beta-lactams.

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