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Activity of Ceftobiprole Tested Against Contemporary European Enterobacteriaceae and *Pseudomonas aeruginosa* (2005-2006)

T.R. Fritsche, H.S. Sader, P.A. Strabala, R.N. Jones
JMI Laboratories, North Liberty, Iowa, USA

Thomas R. Fritsche, MD, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Tel: (319) 665-3370
Fax: (319) 665-3371
e-mail: thomas-fritsche@jmilabs.com

Abstract

Objectives: To present results assessing *in vitro* potency of ceftobiprole (BPR) against the most commonly occurring Enterobacteriaceae (ENT) and non-fermentative Gram-negative bacilli isolates in Europe. BPR, an investigational parenteral cephalosporin, is currently in clinical trials for complicated skin and skin structure infections and pneumonia. This agent is unique amongst its class, being active against methicillin-resistant *Staphylococcus aureus* (MRSA) as well as other Gram-positive and -negative pathogens, making it an attractive candidate for broad-spectrum therapy.

Methods: Non-duplicate, clinically significant isolates of ENT (3399), *Pseudomonas aeruginosa* (PSA; 666), and *Acinetobacter* species (ASP; 230) were collected from 25 medical centres in Europe participating in a BPR surveillance program during 2005-2006. Identifications were confirmed by the central monitoring laboratory and all isolates were susceptibility (S) tested using CLSI methods against BPR and comparators including ceftazidime (CAZ) and cefepime (FEP).

Results: BPR, CAZ, and FEP results are in the Table:

	MIC_{50} (% at ≤2/4/8 mg/L)		
Species (no. tested)	BPR	CAZ	FEP
Escherichia coli (EC; 1889)	≤0.06 (94/94/94)	≤1 (94/95/96)	0.25 (95/95/96)
Klebsiella species (KSP; 624)	>8 (75/75/76)	>16 (78/79/81)	16 (82/85/88)
Enterobacter species (ESP; 381)	>8 (81/84/88)	>16 (66/68/69)	4 (89/94/96)
Citrobacter species (CIT; 79)	1 (99/99/99)	>16 (72/73/76)	1 (99/99/99)
Proteus mirabilis (PM; 143)	≤0.06 (96/96/96)	≤1 (96/97/98)	≤0.12 (97/97/97)
Serratia species (SER; 142)	0.5 (96/96/96)	<1 (96/96/97)	0.5 (98/98/98)
PSA (666)	>8 (54/65/79)	>16 (57/70/76)	16 (49/65/80)
ASP (230)	>8 (37/39/40)	>16 (12/31/37)	>16 (22/33/45)

BPR was similar in potency to the third- and fourth-generation cephems (MIC_{50} values, ≤1 mg/L) for all tested ENT. Coverage against EC was nearly identical for the 3 agents (Table; 94-95% inhibited at ≤4 mg/L). Whereas FEP provided enhanced coverage against KSP (88% at ≤8 mg/L vs. 76-81% for BPR and CAZ), BPR and FEP were superior to CAZ against ESP and CIT. All were equally active against PM, SER and *Salmonella* species. Against PSA, BPR was equal in potency to CAZ (MIC_{50}, 2 mg/L) and 2-fold more potent than FEP, although % inhibited for these agents at ≤2/4/8 mg/L was similar (49-54/65-70/76-80%, respectively). None of these agents inhibited >45% of ASP at 8 mg/L.

Conclusions: Ceftobiprole is a new anti-MRSA β-lactam with recognised activity against the most commonly occurring ENT and PSA, similar to that of extended-spectrum cephems. These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for severe pneumonia, especially in those European institutions/regions where MRSA and PSA may be prevalent.

Introduction

Emergence of resistance among commonly occurring bacterial pathogens has limited the utility of many penicillins and cephalosporins, driving increased utilisation of carbapenems for Gram-negatives and vancomycin, daptomycin, and linezolid for Gram-positives (10, 11). Ceftobiprole, an expanded spectrum cephalosporin with potent activity against commonly occurring Gram-positive and -negative bacterial pathogens (2, 4, 7), including resistant strains, is in late stage (phase 3) clinical development for the treatment of complicated skin and skin structure infections and hospital-acquired pneumonia. The compound is stable to many commonly occurring β-lactamases and has a strong affinity for penicillin-binding proteins, including PBP2' (PBP2a), which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* and coagulase-negative staphylococci. It is therefore an attractive therapeutic candidate given this unique spectrum, broad safety profile characteristic of most β-lactams, and predominant bactericidal activities (3, 7, 8). Ceftobiprole is also known to display *in vitro* activity against most Enterobacteriaceae and *Pseudomonas aeruginosa*, similar to that of advanced generation cephems and β-lactam/β-lactamase inhibitor combinations (9, 12).

Here we assessed current trends in resistance and effects of co-resistance on ceftobiprole potency against the most commonly occurring contemporary (2005-2006) clinical strains of Enterobacteriaceae and non-fermentative Gram-negative bacilli originating from Europe.

Materials and Methods

Bacterial Isolates

Consecutive, non-duplicate clinically significant isolates of Enterobacteriaceae (3399 isolates), *P. aeruginosa* (666) and *Acinetobacter* species (230) were collected from 25 medical centres in European countries participating in a ceftobiprole surveillance program during 2005-2006. Organisms were identified locally and forwarded to a central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) where identifications were confirmed and susceptibility testing using reference methodologies performed. Species and numbers tested during this period are found in **Table 1**.

Susceptibility Test Methods

Ceftobiprole and comparator agents were tested in validated commercial microdilution trays (TREK Diagnostic Systems, Inc., Cleveland, Ohio, USA) using cation-adjusted Mueller-Hinton broth according to CLSI methods (5, 6). Quality control strains utilised included *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853; all MIC results were within CLSI-specified ranges (1). Categorical interpretations were by CLSI M100-S17 breakpoint criteria. Breakpoints have not been approved for ceftobiprole, although this agent is known to have pharmacokinetic and pharmacodynamic features similar to those of other advanced-generation cephalosporins.

Results

- Among all tested Enterobacteriaceae reported here (4154 isolates), ceftobiprole was similar in potency to the expanded spectrum cephems ceftazidime and cefepime (MIC_{50} values, ≤1 mg/L; **Table 1**).
- Ceftobiprole coverage against *E. coli* was nearly identical to that of ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam (not based strictly on MICs), and gentamicin (94-95% inhibited at ≤4 mg/L; **Table 2**).
- Whereas cefepime provided enhanced coverage against *Klebsiella* species (88% at ≤8 mg/L vs 76 to 81% for ceftobiprole and ceftazidime, respectively), ceftobiprole and cefepime were superior to ceftazidime against *Enterobacter* species (88, 96, and 69%, respectively) and *Citrobacter* species (99, 99, and 76%; **Tables 1** and **2**).
- Extended-spectrum β-lactamase (ESBL)-phenotypes were detected among *E. coli* (6.7 to 7.8% for ceftriaxone and ceftazidime, respectively) and *Klebsiella* species (23.7 to 24.4%); ceftobiprole MIC values at ≥2 mg/L for the 2 species were concordant (6.4 and 26.1%, respectively).
- All tested cephalosporins were equally active against *Proteus mirabilis, Serratia marcescens* (**Table 2**) and *Salmonella* species (29 isolates; all MICs ≤1 mg/L).
- Ceftobiprole was equal in potency to ceftazidime against *P. aeruginosa* (MIC_{50}, 2 mg/L) and 2-fold more potent than cefepime based on the MIC_{50}, although the percentage of these agents inhibited at ≤2, 4, and 8 mg/L was similar (49 to 54; 65 to 70; and 76 to 80%, respectively).
- None of these agents inhibited >45% of *Acinetobacter* species at current breakpoints; imipenem was the most potent agent tested (MIC_{50}, 1 mg/L; 63.5% susceptible; **Table 2**).

Table 1. Frequency distributions of 3 cephalosporins tested against ranking European Enterobacteriaceae and non-fermentative bacilli (742 isolates; 2005-2006)

	MIC (mg/L)		Cumulative % inhibited at MIC (mg/L)[a]			
	50%	90%	≤1	2	4	8
Ceftobiprole						
E. coli (1889)	≤0.06	≤0.06	94	94	94	94
Klebsiella species (624)	≤0.06	>8	74	75	75	76
Enterobacter species (381)	≤0.06	>8	77	81	84	88
Citrobacter species (79)	≤0.06	1	94	99	99	99
P. mirabilis (143)	≤0.06	≤0.06	96	96	96	96
Serratia species (142)	≤0.06	0.5	96	96	96	96
P. aeruginosa (666)	2	>8	37	54	65	79
Acinetobacter species (230)	>8	>8	36	37	39	40
Ceftazidime						
E. coli (1889)	≤1	≤1	92	94	95	96
Klebsiella species (624)	≤1	>16	76	78	79	81
Enterobacter species (381)	≤1	>16	61	66	68	69
Citrobacter species (79)	≤1	>16	72	72	73	76
P. mirabilis (143)	≤1	≤1	95	96	97	98
Serratia species (142)	≤1	≤1	91	96	96	97
P. aeruginosa (666)	2	>16	15	57	70	76
Acinetobacter species (230)	>16	>16	6	12	31	37
Cefepime						
E. coli (1889)	≤0.12	0.25	94	95	95	96
Klebsiella species (624)	≤0.12	16	79	82	85	88
Enterobacter species (381)	≤0.12	4	83	89	94	96
Citrobacter species (79)	≤0.12	1	97	99	99	99
P. mirabilis (143)	≤0.12	≤0.12	97	97	97	97
Serratia species (142)	≤0.12	0.5	96	98	98	98
P. aeruginosa (666)	4	16	22	49	65	80
Acinetobacter species (230)	16	>16	13	22	33	45

[a]CLSI breakpoints for susceptibility of the comparison cephalosporins are ≤8 mg/L.

Table 2. *In vitro* activity of ceftobiprole in comparison to selected antimicrobial agents tested against ranking European Enterobacteriaceae and non-fermentative Gram-negative bacilli (2005-2006)

	MIC (mg/L)			% by category[a]	
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible	Resistant
E. coli (1889)					
Ceftobiprole	≤0.06	≤0.06	≤0.06 – >8	–	
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >32	94.1	5.3 (6.7)[b]
Ceftazidime	≤1	≤1	≤1 – >16	95.8	2.3 (7.8)[b]
Cefepime	≤0.12	0.25	≤0.12 – >16	96.3	3.0
Piperacillin-tazobactam	2	8	≤0.5 – >64	93.8	4.5
Imipenem	≤0.12	0.25	≤0.12 – 2	100.0	0.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	79.8	20.2
Gentamicin	≤2	≤2	≤2 – >8	93.4	6.0
Klebsiella species (624)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	–	–
Ceftriaxone	≤0.25	?32	≤0.25 – >32	80.1	13.6 (24.4)[b]
Ceftazidime	≤1	?16	≤1 – >16	81.6	15.4 (23.7)[b]
Cefepime	≤0.12	16	≤0.12 – >16	88.3	8.5
Piperacillin-tazobactam	2	>64	≤0.5 – >64	63.3	22.3
Imipenem	≤0.12	0.25	≤0.12 – >8	98.6	0.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	85.3	12.7
Gentamicin	≤2	?8	≤2 – >8	87.5	11.1
Enterobacter species (381)					
Ceftobiprole	≤0.06	>8	≤0.06 – >8	–	–
Ceftriaxone	≤0.25	?32	≤0.25 – >32	71.9	16.0
Ceftazidime	≤1	?16	≤1 – >16	69.5	25.0
Cefepime	≤0.12	4	≤0.12 – >16	96.3	2.6
Piperacillin-tazobactam	2	64	≤0.5 – >64	75.6	9.2
Imipenem	0.5	2.0	≤0.12 – >8	98.2	1.0
Levofloxacin	≤0.5	>4	≤0.5 – >4	87.9	11.3
Gentamicin	≤2	≤2	≤2 – >8	91.3	7.9
Citrobacter species (79)					
Ceftobiprole	≤0.06	1	≤0.06 – >8	–	–
Ceftriaxone	≤0.25	32	≤0.25 – >32	74.7	6.3
Ceftazidime	≤1	?16	≤1 – >16	75.9	22.8
Cefepime	≤0.12	1	≤0.12 – 16	98.7	0.0
Piperacillin-tazobactam	2	64	≤0.5 – >64	79.7	6.3
Imipenem	0.5	1	≤0.12 – 8	98.7	1.3
Levofloxacin	≤0.5	2	≤0.5 – >4	92.4	6.3
Gentamicin	≤2	≤2	≤2 – >8	92.4	7.6
P. mirabilis (143)					
Ceftobiprole	≤0.06	≤0.06	≤0.06 – >8	–	–
Ceftriaxone	≤0.25	≤0.25	≤0.25 – >32	97.2	2.1
Ceftazidime	≤1	≤1	≤1 – >16	98.6	0.7
Cefepime	≤0.12	≤0.12	≤0.12 – >6	97.2	2.8
Piperacillin-tazobactam	≤0.5	≤0.5	≤0.5 – 64	98.6	0.7
Imipenem	1	2	≤0.12 – >8	99.3	0.7
Levofloxacin	≤0.5	>4	≤0.5 – >4	92.3	6.3
Gentamicin	≤2	≤2	≤2 – >8	93.7	5.6
Serratia species (142)					
Ceftobiprole	≤0.06	0.5	≤0.06 – >8	–	–
Ceftriaxone	≤0.25	8	≤0.25 – >32	90.1	2.1
Ceftazidime	≤1	≤1	≤1 – >16	97.2	2.1
Cefepime	≤0.12	0.5	≤0.12 – >16	98.6	1.4
Piperacillin-tazobactam	2	32	≤0.5 – >64	84.5	1.4
Imipenem	1	1	0.25 – 4	100.0	0.0
Levofloxacin	≤0.5	2	≤0.5 – >4	93.7	2.1
Gentamicin	≤2	≤2	≤2 – >8	93.0	6.3
P. aeruginosa (666)					
Ceftobiprole	2	>8	≤0.06 – >8	–	–
Ceftriaxone	>32	>32	≤0.25 – >32	7.4	62.5
Ceftazidime	2	>16	≤1 – >16	76.1	18.6
Cefepime	4	16	≤0.12 – >16	79.9	9.5
Piperacillin-tazobactam	4	>64	≤0.5 – >64	82.3	17.7
Imipenem	1	>8	≤0.12 – >8	76.6	14.1
Levofloxacin	≤0.5	>4	≤0.5 – >4	69.7	25.8
Gentamicin	≤2	>8	≤2 – >8	77.7	20.6
Acinetobacter species (230)					
Ceftobiprole	>8	>8	≤0.06 – >8	–	–
Ceftriaxone	>32	>32	≤0.25 – >32	20.0	61.7
Ceftazidime	>16	>16	≤1 – >16	37.4	55.7
Cefepime	16	>16	≤0.12 – >16	44.8	37.8
Piperacillin-tazobactam	>64	>64	≤0.5 – >64	37.0	55.2
Imipenem	1	>8	≤0.12 – >8	63.5	33.5
Levofloxacin	4	>4	≤0.5 – >4	38.7	47.4
Gentamicin	>8	>8	≤2 – >8	32.8	64.2

[a]Breakpoint criteria are those of CLSI M100-S17 (6); – = no breakpoints established.
[b]Percentage meeting CLSI criteria for an ESBL-phenotype (≥2 mg/L)

Conclusions

- **Ceftobiprole is a new anti-MRSA β-lactam with recognised activity against the most commonly occurring Enterobacteriaceae and *P. aeruginosa*, similar to that of extended-spectrum cephems.**
- **These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for severe pneumonia, especially in those European institutions/regions where MRSA and *P. aeruginosa* may be prevalent.**

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