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Antimicrobial Activity of Ceftobiprole When Tested against Isolates from Diabetic Foot Infections (2013-2016)

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Abstract

Background: Ceftobiprole medocaril (prodrug of ceftobiprole) is a fifth-generation cephalosporin that is approved for use in multiple European countries to treat hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults. Ceftobiprole medocaril is not approved for use in the United States. In this study the activity of ceftobiprole and comparator agents was evaluated against contemporary clinical isolates from diabetic foot infections (DFI).

Methods: A total of 557 bacterial clinical isolates (1 per patient infection episode) were collected from patients with DFI in 23 medical centers in Europe and 46 medical centers in the US from 2013-2016. Ceftobiprole and comparator agents were susceptibility (S) tested following CLSI methods. Quality control organisms were tested concurrently with clinical isolates. CLSI and EUCAST interpretive criteria were applied according to current guidelines.

Results: Ceftobiprole was very active against *Staphylococcus aureus* (22.9% methicillin-resistant; MRSA); the $MIC_{50/90}$ for ceftobiprole was 0.5/1 mg/L (100.0%S, EUCAST criteria). For methicillin-susceptible *S. aureus*, the $MIC_{50/90}$ was 0.5/0.5 mg/L (100.0% S), and the $MIC_{50/90}$ for MRSA was 1/2 mg/L (100.0%S). Against coagulase-negative staphylococci, the $MIC_{50/90}$ for ceftobiprole was 1/2 mg/L. Ceftobiprole was active against *Enterococcus faecalis* ($MIC_{50/90}$, 0.5/2 mg/L) but not against *E. faecium* (MIC_{50}, >4 mg/L). Against β-haemolytic streptococci, the ceftobiprole $MIC_{50/90}$ was 0.015/0.03 mg/L with all isolates ≤0.03 mg/L. Ceftobiprole S when tested against the *Enterobacteriaceae* was 77.3% (78.0%S, ceftriaxone; 88.7%/92.0%S [EUCAST/CLSI], cefepime). Against *Escherichia coli* ($MIC_{50/90}$, 0.03/>8 mg/L), 77.8%, 77.8%, and 80.6%/83.3% (EUCAST/CLSI) were S to ceftobiprole, ceftriaxone, and cefepime, respectively. For cefepime and ceftazidime, S against *Pseudomonas aeruginosa* was 87.0% and 85.2%, respectively, while 77.8% were inhibited by ≤4 mg/L of ceftobiprole ($MIC_{50/90}$, 2/>8 mg/L).

Conclusions: Ceftobiprole was active against contemporary, clinically relevant Gram-positive and Gram-negative isolates collected at EU and US medical centers from patients with DFI. The activity of ceftobiprole against these isolates was similar to that reported against isolates from other sites of infection. The broad-spectrum activity of ceftobiprole, including *P. aeruginosa* and MRSA, suggests that further studies evaluating the potential of this drug in patients with DFI are justified.

Introduction

- Ceftobiprole is a parenteral fifth-generation cephalosporin that is active against Gram-positive and Gram-negative bacteria
- Ceftobiprole is not approved for use in the US but is currently in Phase 3 development to support indications for acute bacterial skin and skin structure infections and *S. aureus* bacteremia, supported by BARDA; additionally ceftobiprole has received national licenses for the treatment of adult patients with community- and hospital-acquired pneumonia (CAP, HAP), excluding ventilator-associated pneumonia, in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Norway, Spain, Sweden, Switzerland, and the United Kingdom
- Ceftobiprole has shown potent activity in vitro against methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* and has shown activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*
- This agent is administered as the prodrug ceftobiprole medocaril, which is rapidly hydrolyzed *in vivo* to the active form ceftobiprole
- Studies in murine models of infection have shown that the *f*T>MICs required for bactericidal activity of ceftobiprole are ≥30% for Gram-positive and ≥60% *f*T>MIC for Gram-negative organisms
- In a Phase 3 clinical study with HAP patients, ceftobiprole was administered as a 2-hour infusion at a dosage regimen of 500 mg q8h. In this study, the observed target attainments for an MIC of 4 mg/L, the EUCAST PK/PD breakpoint for ceftobiprole, were 100% (N=273) and 96.7% (N=266) at *f*T>MICs of ≥30% and ≥60%, respectively
- Diabetic foot infections are frequent clinical problems that may be caused by many organisms in either single or polymicrobic infections, and are often caused by Gram-positive bacteria, especially *S. aureus*
- In this study, ceftobiprole activity was evaluated against bacterial isolates from the US and Europe collected during 2013 through 2016 from patients with diabetic foot infections

Materials and Methods

- A total of 557 bacterial isolates (304 from Europe and 253 from the US) were collected prospectively from patients during 2013 through 2016 in 23 medical centers in Europe and 46 medical centers in the US as part of the SENTRY Antimicrobial Surveillance Program
  - Isolates selected for this study were designated by the site as pathogens isolated from diabetic foot infections
  - These were nonduplicate isolates from patients with a diabetic foot infection
  - Species identification was performed at the participant medical centers and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using standard biochemical tests or matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA), following the manufacturer's instructions
- Clinical isolates and quality control organisms were tested for susceptibility to ceftobiprole and comparators according to CLSI guidelines using broth microdilution panels
- CLSI (2017) and EUCAST (2017) interpretive criteria were applied
- Quality control organisms were tested concurrently with clinical isolates

Results

- The pathogens most commonly isolated from diabetic foot infections were *S. aureus* (including MRSA), β-haemolytic streptococci, *Enterobacteriaceae*, and *P. aeruginosa*
- Ceftobiprole was highly active against 223 *S. aureus* isolates
  - All were susceptible to ceftobiprole (EUCAST interpretive criteria; susceptible ≤2 mg/L) and 98.2% were susceptible to ceftaroline
  - The $MIC_{50/90}$ values for ceftobiprole and ceftaroline were 0.5/1 mg/L and 0.25/1 mg/L, respectively
  - A total of 22.9% of *S. aureus* were methicillin-resistant
  - Against MRSA, the ceftobiprole $MIC_{50/90}$ values were 1/2 mg/L and the ceftaroline values were 1/1 mg/L
  - Resistance rates for MRSA were much higher than for MSSA with levofloxacin (62.7% vs 4.7%; CLSI), erythromycin (80.4% vs 18.0%; CLSI), and clindamycin (39.2% vs 5.2%; CLSI)
- In the absence of breakpoints for coagulase-negative staphylococci, applying the defined EUCAST *Staphylococcus* spp. (*S. aureus*) breakpoints of 1 mg/L for ceftaroline and 2 mg/L for ceftobiprole for analysis purposes, all coagulase-negative staphylococci were susceptible to ceftaroline and 90.5% were susceptible to ceftobiprole
  - A total of 57.1% of coagulase-negative staphylococci were methicillin-resistant
- Ceftobiprole exhibited potent activity against *Enterococcus faecalis* ($MIC_{50/90}$, 0.5/2mg/L), which was 4-fold more active than ceftaroline ($MIC_{50/90}$, 2/8 mg/L)
- Both ceftobiprole and ceftaroline exhibited poor activity against *E. faecium* (MIC_{50}, >4mg/L)
- Against the β-haemolytic streptococci, ceftaroline ($MIC_{50/90}$, ≤0.015/≤0.015 mg/L) and ceftobiprole ($MIC_{50/90}$, 0.015/0.03 mg/L) were highly potent, as were other β-lactams
  - The highest ceftobiprole MIC was 0.03 mg/L
- Ceftobiprole activity against *Enterobacteriaceae* (77.3% susceptible) was more similar to that of ceftriaxone (78.0%/78.0%; EUCAST/CLSI criteria) or ceftazidime (80.0%/86.7%, EUCAST/CLSI criteria) than to ceftaroline (64.9%; EUCAST/CLSI)
- When tested against *P. aeruginosa*, the percentage of ceftobiprole MIC values that were ≤2 mg/L and ≤4 mg/L were 64.8% and 77.8%, respectively
  - Susceptibility for ceftazidime was 85.2% (CLSI) and for cefepime 87.0% (CLSI)

Table 1 Antimicrobial activity of ceftobiprole tested against the main organisms and organism groups of isolates (mg/L)

Organism / organism group	No. of isolates at MIC (mg/L; cumulative %)													MIC_{50}	MIC_{90}
	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>		
S. aureus (223)				1 (0.4%)	0 (0.4%)	0 (0.4%)	74 (33.6%)	100 (78.5%)	33 (93.3%)	15 (100.0%)				0.5	1
MRSA (51)							0 (0.0%)	3 (5.9%)	33 (70.6%)	15 (100.0%)				1	2
MSSA (172)				1 (0.6%)	0 (0.6%)	0 (0.6%)	74 (43.6%)	97 (100.0%)						0.5	0.5
CoNS (21)				0 (0.0%)	1 (4.8%)	4 (23.8%)	0 (23.8%)	1 (28.6%)	11 (81.0%)	2 (90.5%)	2 (100.0%)			1	2
E. faecalis (24)						2 (8.3%)	7 (37.5%)	6 (70.8%)	3 (83.3%)	2 (91.7%)	2 (100.0%)			0.5	2
E. faecium (7)								0 (0.0%)	1 (14.3%)	0 (14.3%)	0 (14.3%)		6 (100.0%)	>4	—
β-haemolytic streptococci (58)		19 (32.8%)	14 (56.9%)	25 (100.0%)										0.015	0.03
S. pyogenes (12)		9 (75.0%)	2 (91.7%)	1 (100.0%)										≤0.008	0.015
S. agalactiae (33)	0 (0.0%)	1 (3.0%)	8 (27.3%)	24 (100.0%)										0.03	0.03
Enterobacteriaceae (150)		3 (2.0%)	13 (10.7%)	73 (59.3%)	17 (70.7%)	4 (73.3%)	6 (77.3%)	6 (81.3%)	1 (82.0%)	1 (82.7%)	0 (82.7%)	0 (82.7%)	26 (100.0%)	0.03	>8
E. coli (36)		0 (0.0%)	1 (2.8%)	24 (69.4%)	3 (77.8%)	0 (77.8%)	0 (77.8%)	0 (77.8%)	0 (77.8%)	1 (80.6%)	0 (80.6%)	0 (80.6%)	7 (100.0%)	0.03	>8
Enterobacter spp. (22)			0 (0.0%)	9 (40.9%)	5 (63.6%)	1 (68.2%)	1 (72.7%)	2 (81.8%)	0 (81.8%)	0 (81.8%)	0 (81.8%)	0 (81.8%)	4 (100.0%)	0.06	>8
Klebsiella spp. (21)		0 (0.0%)	2 (9.5%)	5 (33.3%)	4 (52.4%)	1 (57.1%)	3 (71.4%)	2 (81.0%)	0 (81.0%)	0 (81.0%)	0 (81.0%)	0 (81.0%)	4 (100.0%)	0.06	>8
K. pneumoniae (14)		0 (0.0%)	2 (14.3%)	5 (50.0%)	3 (71.4%)	0 (71.4%)	1 (78.6%)	0 (78.6%)	0 (78.6%)	0 (78.6%)	0 (78.6%)	0 (78.6%)	3 (100.0%)	0.03	>8
P. aeruginosa (54)							0 (0.0%)	3 (5.6%)	11 (25.9%)	21 (64.8%)	7 (77.8%)	5 (87.0%)	7 (100.0%)	2	>8

Table 2 Activity of ceftobiprole and comparator antimicrobial agents when tested against diabetic foot infection isolates (2013-2016)

Organism (no.) / antimicrobial agent	MIC_{50}	MIC_{90}	CLSI* %S	CLSI* %R	EUCAST* %S	EUCAST* %R
***S. aureus* (223)**						
Ceftobiprole	0.5	1	—	—	100.0	0.0
Ceftaroline	0.25	1	98.2	0.0	98.2	1.8
Ceftriaxone	4	>8	77.1	22.9	—	—
Clindamycin	≤0.25	>2	86.5	13.0	86.5	13.5
Doxycycline	≤0.06	0.12	97.3	0.0	96.0	3.1
Erythromycin	0.25	>8	63.2	32.3	64.1	34.5
Gentamicin	≤1	≤1	98.7	1.3	98.7	1.3
Levofloxacin	0.25	>4	82.1	17.9	82.1	17.9
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	0.5	>2	77.1	22.9	77.1	22.9
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	99.1	0.9	99.1	0.4
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MRSA (51)						
Ceftobiprole	1	2	—	—	100.0	0.0
Ceftaroline	1	1	92.2	0.0	92.2	7.8
Clindamycin	≤0.25	>2	60.8	39.2	60.8	39.2
Doxycycline	≤0.06	0.5	92.2	0.0	92.2	7.8
Erythromycin	>8	>8	17.6	80.4	17.6	80.4
Gentamicin	≤1	≤1	98.0	2.0	98.0	2.0
Levofloxacin	4	>4	37.3	62.7	37.3	62.7
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	0.0	100.0	0.0	100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	96.1	3.9	96.1	2.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MSSA (172)						
Ceftobiprole	0.5	0.5	—	—	100.0	0.0
Ceftaroline	0.25	0.25	100.0	0.0	100.0	0.0
Ceftriaxone	4	4	100.0	0.0	—	—
Clindamycin	≤0.25	≤0.25	94.2	5.2	94.2	5.8
Doxycycline	≤0.06	0.12	98.8	0.0	97.1	1.7
Erythromycin	0.25	>8	76.7	18.0	77.9	20.9
Gentamicin	≤1	≤1	98.8	1.2	98.8	1.2
Levofloxacin	≤0.12	0.25	95.3	4.7	95.3	4.7
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	0.5	0.5	100.0	0.0	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	100.0	0.0	100.0	0.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
CONS (21)						
Ceftobiprole	1	2	—	—	—	—
Ceftaroline	0.5	1	—	—	—	—
Ceftriaxone	>8	>8	42.9	57.1	—	—
Clindamycin	>2	>2	47.6	52.4	47.6	52.4
Doxycycline	≤0.06	4	90.5	9.5	85.7	14.3
Erythromycin	>8	>8	28.6	71.4	28.6	71.4
Gentamicin	≤1	>8	52.4	33.3	52.4	47.6
Levofloxacin	0.5	>4	52.4	38.1	52.4	38.1
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Oxacillin	>2	>2	42.9	57.1	42.9	57.1
Trimethoprim-sulfamethoxazole	2	>4	52.4	47.6	52.4	33.3
Vancomycin	1	2	100.0	0.0	100.0	0.0
***E. faecalis* (24)**						
Ceftobiprole	0.5	2	—	—	—	—
Ceftaroline	2	8	—	—	—	—
Ampicillin	1	2	100.0	0.0	100.0	0.0
Daptomycin	0.5	1	100.0	—	—	—
Doxycycline	8	—	33.3	16.7	—	—
Levofloxacin	1	>4	70.8	29.2	70.8	29.2
Linezolid	1	1	100.0	0.0	100.0	0.0
Vancomycin	1	2	100.0	0.0	100.0	0.0
β-haemolytic streptococci (58)						
Ceftobiprole	0.015	0.03	—	—	—	—
Ceftaroline	≤0.015	≤0.015	100.0	—	100.0	0.0
Ceftriaxone	≤0.06	0.12	100.0	—	100.0	0.0
Clindamycin	≤0.25	>2	87.7	12.3	87.7	12.3
Erythromycin	≤0.12	>4	62.1	34.5	62.1	34.5
Levofloxacin	0.5	1	98.3	1.7	94.8	5.2
Linezolid	1	1	100.0	—	100.0	0.0
Penicillin	≤0.06	≤0.06	100.0	—	100.0	0.0
Tetracycline	>8	>8	43.1	55.2	41.4	56.9
Vancomycin	0.25	0.5	100.0	—	100.0	0.0
***Enterobacteriaceae* (150)**						
Ceftobiprole	0.03	>8	—	—	77.3	22.7
Cefepime	≤0.5	2	92.0	6.0	88.7	6.7
Ceftaroline	0.25	>32	64.9	—	64.9	35.1
Ceftazidime	0.25	32	86.7	12.0	80.0	13.3
Ceftriaxone	0.12	>8	78.0	18.7	78.0	18.7
Aztreonam	≤0.12	16	85.9	11.4	81.2	14.1
Doxycycline	2	>8	57.3	32.0	—	—
Gentamicin	≤1	>8	88.7	10.7	85.3	11.3
Levofloxacin	≤0.12	>4	76.0	20.0	72.7	24.0
Meropenem	≤0.06	≤0.06	99.3	0.7	99.3	0.7
Piperacillin-tazobactam	2	16	91.3	4.7	88.7	8.7
Trimethoprim-sulfamethoxazole	≤0.5	>4	69.3	30.7	69.3	29.3
***E. coli* (36)**						
Ceftobiprole	0.03	>8	—	—	77.8	22.2
Cefepime	≤0.5	>16	83.3	11.1	80.6	13.9
Ceftaroline	0.12	>32	75.0	22.2	75.0	25.0
Ceftazidime	0.25	32	86.1	13.9	80.6	13.9
Ceftriaxone	≤0.06	>8	77.8	22.2	77.8	22.2
Aztreonam	≤0.12	>16	83.3	13.9	77.8	16.7
Doxycycline	4	>8	52.8	27.8	—	—
Gentamicin	≤1	>8	83.3	16.7	83.3	16.7
Levofloxacin	≤0.12	>4	61.1	33.3	61.1	38.9
Meropenem	≤0.06	≤0.06	100.0	0.0	100.0	0.0
Piperacillin-tazobactam	2	8	94.4	2.8	91.7	5.6
Trimethoprim-sulfamethoxazole	≤0.5	>4	52.8	47.2	52.8	44.4
***K. pneumoniae* (14)**						
Ceftobiprole	0.03	>8	—	—	78.6	21.4
Cefepime	≤0.5	>16	78.6	21.4	71.4	21.4
Ceftaroline	0.06	>32	57.1	35.7	57.1	42.9
Ceftazidime	0.25	>32	78.6	21.4	78.6	21.4
Ceftriaxone	≤0.06	>8	78.6	21.4	78.6	21.4
Aztreonam	≤0.12	>16	78.6	21.4	78.6	21.4
Doxycycline	2	>8	64.3	28.6	—	—
Gentamicin	≤1	≤1	92.9	7.1	92.9	7.1
Levofloxacin	≤0.12	>4	85.7	14.3	78.6	14.3
Meropenem	≤0.06	≤0.06	92.9	7.1	92.9	7.1
Piperacillin-tazobactam	2	>64	64.3	28.6	57.1	35.7
Trimethoprim-sulfamethoxazole	≤0.5	>4	78.6	21.4	78.6	21.4
***P. aeruginosa* (54)**						
Ceftobiprole	2	>8	—	—	—	—
Cefepime	2	16	87.0	5.6	87.0	13.0
Ceftazidime	2	32	85.2	11.1	85.2	14.8
Amikacin	2	8	92.6	3.7	90.7	7.4
Gentamicin	≤1	>8	87.0	11.1	87.0	13.0
Aztreonam	8	>16	83.0	20.4	83.0	20.4
Levofloxacin	0.5	>4	77.8	20.4	72.2	22.2
Meropenem	0.5	4	87.0	5.6	87.0	5.6
Piperacillin-tazobactam	4	64	83.3	7.4	83.3	16.7
Tobramycin	0.5	>8	88.9	11.1	88.9	11.1

* Criteria as published by CLSI [2017] and EUCAST [2017]
* — , No interpretive criteria

Conclusions

- Ceftobiprole is an advanced cephalosporin that demonstrates potent activity against *S. aureus*, including MRSA, and β-haemolytic streptococci, while maintaining activity against Gram-negative bacteria
- The pathogens most commonly isolated from diabetic foot infections were *S. aureus* (including MRSA), which represented 40.0% of isolates, followed by *Enterobacteriaceae* (26.9%), β-haemolytic streptococci (10.4%), and *P. aeruginosa* (9.7%)
- The potent activity demonstrated by ceftobiprole against Gram-positive and Gram-negative bacteria isolated from contemporary diabetic foot infections warrants further study for the potential use of ceftobiprole in these infections
- Evaluating the ceftobiprole pharmacokinetics in patients with diabetic foot infections would help determine its potential role

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