POSTER 781
ECCMID 2007

Activity of Ceftobiprole Tested Against Staphylococcal and Streptococcal Isolates Recovered From Patients in European Medical Centres (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

Updated* Abstract

Objectives: To present *in vitro* potency of ceftobiprole (BPR) against staphylococci and streptococci originating from European (EUR) patients in 2005 and 2006. BPR, an investigational parenteral cephalosporin with a broad spectrum against Gram-negative and -positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), is currently in clinical trials targeting complicated skin and skin structure infections (cSSSI) and pneumonia.

Methods: Non-duplicate clinically-significant isolates (5827 isolates) of *S. aureus* (SA; oxacillin-susceptible [OXA-S] and -resistant [R]), coagulase-negative staphylococci (CoNS; OX-S, and OX-R), *Streptococcus pneumoniae* (SPN; penicillin [PEN]-S and PEN-R), viridans group streptococci (VGS), and β-haemolytic streptococci (BHS) were submitted from 25 medical centres in EUR participating in BPR surveillance (2005-2006). Central laboratory processing included identification confirmation and susceptibility (S) testing to BPR and other comparative β-lactams using CLSI reference methods and interpretive criteria.

Results:

	BPR MIC (mg/L)		Cum. % inhibited at MIC (mg/L)					
Organism (no. tested)	50%	90%	≤0.12	0.25	0.5	1	2	4
SA								
OXA-S (1917)	0.25	0.5	3	74	>99	>99	100	
OXA-R (781)	1	2	<1	<1	16	65	96	100
CoNS								
OXA-S (324)	0.12	0.25	68	97	100			
OXA-R (826)	1	2	1	7	42	81	93	>99
SPN								
PEN-S (845)	≤0.06	≤0.06	100					
PEN-R (169)	0.25	0.5	1	55	100			
VGS (289)	≤0.06	0.25	89	92	94	95	96	97
BHS (509)	≤0.06	≤0.06	>99	100				

BPR inhibited 100 and >99% of tested *S. aureus* and CoNS at ≤4 mg/L, respectively, and all SPN and BHS at ≤0.5 mg/L. While MIC_{90} values for OXA-R strains were 4- and 8-fold higher for SA and CoNS, respectively, published PK/PD characteristics suggest that target attainment for both OXA-S and -R populations would be achievable. BPR potency against OXA-S and OXA-R SA from North America and Latin America were nearly identical to those presented here for EUR ($MIC_{50/90}$, 0.25/0.5 and 1-2/2 mg/L, respectively). All streptococci were readily inhibited by BPR (MIC_{90} values ≤0.5 mg/L); only VGS included strains with elevated MIC values (6% at >0.5 mg/L). BPR potency against SPN was equivalent to that of imipenem (MIC_{90}, 0.25 mg/L). While BPR is generally inactive against *Enterococcus faecium*, the majority of *E. faecalis* strains (93% of 720 isolates) were inhibited at ≤4 mg/L (data not shown).

Conclusions: Ceftobiprole displayed an antibacterial spectrum of activity against EUR pathogens responsible for cSSSI and NP, including OXA-R SA and OXA-R CoNS. Ceftobiprole was also among the most active β-lactams tested against SPN, equivalent in potency to the carbapenems.

*Updated to modify strain numbers

Introduction

Ceftobiprole (previously known as BAL9141) is an anti–methicillin-resistant *Staphylococcus aureus* (MRSA) cephalosporin with potent activity against Gram-positive and -negative bacteria (3, 6). Ceftobiprole is stable to many β-lactamases and has a strong affinity for penicillin binding proteins, including PBP2' (PBP2a), which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *S. aureus* and coagulase-negative staphylococci, and PBP2x, which is associated with penicillin resistance in pneumococci. Ceftobiprole is therefore an attractive therapeutic candidate given this unique spectrum, its safety profile characteristic of most β-lactams, and its predominantly bactericidal activity (2, 6, 7). Ceftobiprole also displays antibacterial activity against Enterobacteriaceae and many *Pseudomonas aeruginosa* isolates, similar to that of other advanced generation cephalosporins (8). The agent is currently in late stage clinical development (phase 3) for the treatment of complicated skin and skin structure infections and hospital-acquired as well as community-acquired pneumonia.

The objective of the current study was to examine the susceptibility profiles and antibiograms of ceftobiprole and comparator agents tested against contemporary European clinical isolates of staphylococci and streptococci collected in 2005-2006 as part of a longitudinal international resistance surveillance protocol. A total of 5827 strains were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI) with susceptibilities interpreted by current CLSI criteria (2007).

Materials and Methods

Bacterial Isolates

Consecutive, non-duplicate clinically significant isolates of *S. aureus* (2698 strains), coagulase-negative staphylococci (1150), *Streptococcus pneumoniae* (1181), viridans group streptococci (289), and β-haemolytic streptococci (509) were submitted from 25 medical centres in Europe as part of a global antimicrobial resistance surveillance network and tested in a central laboratory (JMI Laboratories, North Liberty, Iowa, USA) using reference methodologies. Further analyses were performed on specific resistant subsets (oxacillin for staphylococci and penicillin for *S. pneumoniae*).

Susceptibility Test Methods

The susceptibility profiles of the strain collection were determined using validated broth microdilution test panels (TREK Diagnostic Systems, Inc., Cleveland, Ohio, USA) according to CLSI methods and interpretive criteria (4, 5). MIC tests were performed in cation-adjusted Mueller-Hinton broth (with the addition of 2-5% lysed horse blood for testing of streptococci). Quality control (QC) strains utilised included *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 (1, 5); all QC MIC results were within CLSI-specified ranges.

Table 1. Antimicrobial activity of ceftobiprole and selected comparison agents tested against *S. aureus*, coagulase-negative staphylococci and streptococci recovered from patients in European medical centres (2005-2006)

	MIC (mg/L)				
Organism (no. tested)	50%	90%	Range	%S[a]	%R[a]
S. aureus (2698)					
Ceftobiprole	0.25	2	≤0.06 – 4	–	–
Oxacillin	0.5	>2	≤0.25 – >2	71.1	28.9
Ciprofloxacin	0.5	>4	≤0.03 – >4	67.1	32.1
Erythromycin	≤0.25	>2	≤0.25 – >2	68.6	30.8
Clindamycin	≤0.25	>2	≤0.25 – >2	85.3	14.5
Linezolid	1	2	0.12 – 2	100.0	–
Daptomycin	0.25	0.5	≤0.06 – 1	100.0	–
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25 – >2	99.5	0.4
Tetracycline	≤2	≤2	≤2 – >8	90.9	8.4
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	98.5	0.5
Vancomycin	1	1	≤0.12 – 2	100.0	0.0
Coagulase-negative staphylococci (1150)					
Ceftobiprole	0.5	2	≤0.06 – 8	–	–
Oxacillin	>2	>2	≤0.25 – >2	28.2	71.8
Ciprofloxacin	4	>4	≤0.03 – >4	44.3	51.6
Erythromycin	>2	>2	≤0.25 – >2	37.3	62.3
Clindamycin	≤0.25	>2	≤0.25 – >2	75.9	23.1
Linezolid	1	1	≤0.06 – 8	99.9	–
Daptomycin	0.25	0.5	≤0.06 – 4	99.9	–
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25 – 2	99.0	0.4
Tetracycline	≤2	>8	≤2 – >8	80.2	18.3
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5 – >2	62.9	37.1
Vancomycin	1	2	≤0.12 – 4	100.0	0.0
S. pneumoniae (1181)					
Ceftobiprole	≤0.06	0.25	≤0.06 – 0.5	–	–
Penicillin	≤0.03	2	≤0.03 – 4	71.5	14.3
Ceftriaxone	≤0.25	1	≤0.25 – 8	88.0[b]	1.1[b]
Levofloxacin	1	1	≤0.5 – >4	97.5	2.3
Erythromycin	≤0.25	>2	≤0.25 – >2	67.9	31.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	78.1	21.3
Linezolid	1	1	≤0.12 – 2	100.0	–
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25 – >2	99.5	0.5
Tetracycline	≤2	>8	≤2 – >8	74.3	24.3
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5 – >2	64.6	22.5
Vancomycin	≤1	≤1	≤1	100.0	–
Viridans group streptococci (289)					
Ceftobiprole	≤0.06	0.25	≤0.06 – >8	–	–
Penicillin	0.06	0.5	≤0.016 – >32	81.7	6.2
Ceftriaxone	≤0.25	1	≤0.25 – >32	90.0	6.6
Levofloxacin	1	1	≤0.5 – >4	96.9	2.4
Erythromycin	≤0.25	>2	≤0.25 – >2	64.4	33.6
Clindamycin	≤0.25	>2	≤0.25 – >2	87.2	12.8
Linezolid	0.5	1	≤0.06 – 2	100.0	–
Quinupristin-dalfopristin	0.5	1	≤0.25 – >2	97.6	0.3
Tetracycline	≤2	>8	≤2 – >8	65.4	32.9
Trimethoprim-sulfamethoxazole	≤0.5	2	≤0.5 – >2	–	–
Vancomycin	0.5	0.5	≤0.12 – >16	99.3	–
β-haemolytic streptococci (509)					
Ceftobiprole	≤0.06	<0.06	≤0.06 – 0.25	–	–
Penicillin	≤0.016	0.06	≤0.016 – 0.06	100.0	–
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0	–
Levofloxacin	≤0.5	1	≤0.5 – >4	99.8	0.2
Erythromycin	≤0.25	>2	≤0.25 – >2	76.6	22.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.0	9.0
Linezolid	1	1	0.25 – 1	100.0	–
Quinupristin-dalfopristin	≤0.25	≤0.25	≤0.25 – 1	100.0	0.0
Tetracycline	≤2	>8	≤2 – >8	53.2	44.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5 – 2	–	–
Vancomycin	0.25	0.5	≤0.12 – 1	100.0	–

[a] Susceptibility breakpoint criteria of the CLSI [2007]; for ceftobiprole, susceptible breakpoints of ≤4 mg/L for staphylococci and ≤1 mg/L for *S. pneumoniae* and other streptococci were used for comparative purposes only; – = no established breakpoints.
[b] Meningitis breakpoints as specified by CLSI [2007].

Table 2. Antimicrobial activity of ceftobiprole tested against *S. aureus* coagulase-negative staphylococci and streptococci, including resistant subsets, recovered from patients in European medical centres (2005-2006)

	MIC (mg/L)		Cumulative % inhibited at MIC (mg/L)					
Organism (no. tested)	50%	90%	≤0.12	0.25	0.5	1	2	4
S. aureus								
Oxacillin-susceptible (1917)	0.25	0.5	3	74	>99	>99	100	–
Oxacillin-resistant (781)	1	2	<1	<1	16	65	96	100
Coagulase negative staphylococci								
Oxacillin-susceptible (324)	0.12	0.25	68	97	100	–	–	–
Oxacillin-resistant (826)	1	2	1	7	42	81	93	>99
S. pneumoniae								
Penicillin-susceptible (845)	≤0.06	≤0.06	100	–	–	–	–	–
Penicillin-resistant (169)	0.25	0.5	1	55	100	–	–	–
Viridans group streptococci (289)	≤0.06	0.25	89	92	94	95	96	97
β-haemolytic streptococci (509)	≤0.06	≤0.06	>99	100	–	–	–	–

Results

- Ceftobiprole inhibited 100 and >99% of tested *S. aureus* and coagulase-negative staphylococci at ≤4 mg/L, respectively; only one coagulase-negative *Staphylococcus* strain had a ceftobiprole MIC of 8 mg/L (**Tables 1** and **2**).
- All *S. pneumoniae* and β-haemolytic streptococci were inhibited by ≤0.5 mg/L of ceftobiprole, as well as 94% of viridans group streptococci (**Table 2**).
- Ceftobiprole MIC_{90} values for oxacillin-resistant strains were 4- and 8-fold higher than for oxacillin-susceptible *S. aureus* and coagulase-negative staphylococci, respectively, but >99% of the isolates were inhibited at MICs <4 mg/L.
- Ceftobiprole potency against oxacillin-susceptible and -resistant *S. aureus* from North America and Latin America were nearly identical to those presented here for European strains ($MIC_{50/90}$, 0.25/0.5 and 1-2/2 mg/L, respectively; data not shown).
- Vancomycin, daptomycin, and linezolid retained near-complete (≥99.9%) coverage when tested against this large collection of European staphylococci.
- While ceftobiprole is generally inactive against *Enterococcus faecium*, the majority of *E. faecalis* strains (93% of 720 isolates) were inhibited at ≤4 mg/L (data not shown).

Conclusions

- **Among Gram-positive bacterial pathogens recovered from patients hospitalised in European medical centres (2005-2006), ceftobiprole inhibited all tested *S. aureus* at ≤4 mg/L, coagulase-negative staphylococci at ≤8 mg/L, and *S. pneumoniae* and β-haemolytic streptococci at 0.5 mg/L.**
- **While potency of ceftobiprole against resistant subsets was decreased (4- to 8-fold for oxacillin-resistant staphylococci and 8-fold for penicillin-resistant pneumococci), the majority (>99%) of key Gram-positive pathogens would be expected to be inhibited at achievable *in vivo* concentrations partly based upon MIC population distributions.**
- **Ceftobiprole displays potent activity against leading pathogens responsible for skin and skin structure infections and community-associated respiratory infections in Europe, and was unique among cephalosporins in retaining activity against pathogens routinely resistant to other β-lactam antimicrobials.**

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