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Spectrum and Potency of Ceftobiprole Tested Against Staphylococci and Streptococci Recovered From Patients in Latin America (2005)

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Updated Abstract

Background: Ceftobiprole (BAL9141; BPR), a developmental parenteral cephalosporin with a broad spectrum including MRSA, has demonstrated efficacy in infections of skin and skin structures (SSSI). We present results assessing *in-vitro* potency of BPR against staphylococci and streptococci originating from Latin American patients.

Methods: Nonduplicate clinically-significant isolates (1103 isolates) of *S. aureus* (SA; oxacillin-susceptible [OXA-S] and -resistant [R]), coagulase-negative staphylococci (CoNS; OXA-S and OXA-R), *S. pneumoniae* (SPN; penicillin (PEN)-S and PEN-R), viridans group streptococci (VGS) and β-hemolytic streptococci (BHS) were submitted from 10 medical centers in Latin America (LA) participating in BPR surveillance (2005). Identifications were confirmed by the central monitor and all isolates were tested for susceptibility (S) using CLSI methods.

Results[a]:

	BPR MIC (µg/ml)		Cum. % inhibited at MIC (µg/ml)					
Organism (no. tested)	50%	90%	≤0.12	0.25	0.5	1	2	4
SA								
OXA-S (363)	0.25	0.5	2	61	>99	>99	100	-
OXA-R (147)	2	2	0	<1	7	30	96	100
CoNS								
OXA-S (40)	0.12	0.25	50	100	-	-	-	-
OXA-R (143)	1	2	3	12	34	66	92	98
SPN								
PEN-S (211)	≤0.06	≤0.06	100	-	-	-	-	-
PEN-R (43)	0.25	0.5	7	63	100	-	-	-
VGS (24)	≤0.06	0.25	87	92	100	-	-	-
BHS (77)	≤0.06	≤0.06	100	-	-	-	-	-

BPR inhibited 100% of tested *S. aureus* at 4 µg/ml and streptococci at 0.5 µg/ml. 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 are achievable. BPR potency against OXA-S and OXA-R SA from North America were nearly identical to those presented here ($MIC_{50/90}$, 0.25/0.5 and 1/2 µg/ml, respectively). All streptococci were readily inhibited by BPR (MIC_{90} values ≤0.25), including PEN-R strains.

Conclusions: Ceftobiprole displays potent activity against the leading staphylococci and streptococci responsible for SSSI in Latin America, and is unique in retaining activity against pathogens resistant to other β-lactam antimicrobial agents.

[a]Updated to include additional strains.

Introduction

Ceftobiprole (previously known as BAL9141), an investigational broad-spectrum cephalosporin with potent *in-vitro* and *in-vivo* activity against Gram-positive and -negative bacteria (3, 7, 9) is in late stage (phase 3) clinical development for the treatment of complicated skin and skin structure infections and hospital-acquired pneumonia. Ceftobiprole is stable to many β-lactamases and has a strong affinity for penicillin-binding proteins, including PBP2a, which mediates resistance to β-lactams in methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (CoNS) (9), and PBP2x, which is associated with penicillin resistance in pneumococci (6). This makes ceftobiprole an attractive therapeutic candidate given this unique spectrum, broad safety profile characteristic of most β-lactams, and predominant bactericidal activities (2, 7, 8, 10). Ceftobiprole also displays activity against Enterobacteriaceae and many *Pseudomonas aeruginosa* isolates, similar to that of advanced generation cephalosporins. Current clinical trials are investigating the use of ceftobiprole.

The objective of the current study was to examine the susceptibility profiles and antibiograms of ceftobiprole and comparator agents tested against contemporary clinical isolates of staphylococci and streptococci collected in 2005 as part of a longitudinal international surveillance protocol. A total of 1103 strains were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI) with susceptibilities interpreted by current CLSI criteria.

Materials and Methods

Bacterial Isolates

- Consecutive, nonduplicate clinically significant isolates of the following were submitted from 10 laboratories in Latin America (Argentina, 2 sites; Brazil, 4 sites; Chile, 2 sites; Mexico, 2 sites) as part of a global antimicrobial resistance surveillance network.
  - *S. aureus* (510 strains)
  - CoNS (183)
  - *Streptococcus pneumoniae* (309)
  - Viridans group streptococci (24)
  - β-hemolytic streptococci (77)
- The isolates were 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 (4) and interpretive criteria (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 strains utilized included *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 (1, 5); all MIC results were within CLSI-specified ranges (5).

Table 1. Antimicrobial activity of ceftobiprole and selected comparison agents tested against *S. aureus*, CoNS, and streptococci recovered from patients in Latin American medical centers (2005)

	MIC (µg/ml)				
Organism (no. tested)	50%	90%	Range	% Susceptible[a]	% Resistant[a]
S. aureus (510)					
Ceftobiprole	0.5	2	≤0.06 – 4	–	–
Oxacillin	0.5	>2	≤0.25 – >2	71.2	28.8
Ciprofloxacin	0.25	>4	≤0.03 – >4	70.4	28.8
Erythromycin	≤0.25	>2	≤0.25 – >2	63.3	36.7[b]
Clindamycin	≤0.25	>2	≤0.25 – >2	73.3	26.5
Linezolid	1	2	0.25 – 2	100.0	0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0	–
Quinupristin-dalfopristin	≤0.25	0.5	≤.25 – 1	100.0	0.0
Tetracycline	≤2	>8	≤2 – >8	81.4	17.1
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5 – >2	86.1	13.9
Vancomycin	1	1	0.5 – 2	100.0	0.0
CoNS (183)					
Ceftobiprole	1	2	≤0.06 – 8	–	–
Oxacillin	>2	>2	≤0.25 – >2	21.9	78.1
Ciprofloxacin	4	>4	≤0.03 – >4	45.9	50.8
Erythromycin	>2	>2	≤0.25 – >2	32.2	67.2[b]
Clindamycin	2	>2	≤0.25 – >2	49.2	49.2
Linezolid	1	1	0.12 – 2	100.0	–
Daptomycin	0.25	0.5	≤0.06 – 1	100.0	–
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25 – 2	98.9	0.0
Tetracycline	≤2	>8	≤2 – >8	82.0	16.9
Trimethoprim-sulfamethoxazole	2	>2	≤0.5 – >2	51.4	48.6
Vancomycin	1	2	0.25 – 4	100.0	0.0
S. pneumoniae (309)					
Ceftobiprole	≤0.06	0.25	≤0.06 – 0.5	–	–
Penicillin	≤0.03	2	≤0.03 – >4	68.3	13.9
Ceftriaxone	≤0.25	1	≤0.25 – 2	88.7	1.0[c]
Levofloxacin	1	1	≤0.5 – 2	100.0	0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.2	17.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.1	3.9
Linezolid	1	1	≤0.12 – 2	100.0	–
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25 – 0.5	100.0	0.0
Tetracycline	≤2	>8	≤2 – >8	84.5	13.9
Trimethoprim-sulfamethoxazole	≤0.5	>2	≤0.5 – >2	61.8	29.1
Vancomycin	≤1	≤1	≤1	100.0	–
Viridans group streptococci (24)					
Ceftobiprole	≤0.06	0.25	0.06 – 0.5	–	–
Penicillin	0.06	0.5	0.016 – 8	75.0	4.2
Ceftriaxone	≤0.25	1	0.25 – 4	91.7	0.0
Levofloxacin	1	1	0.5 – 4	95.8	37.5
Erythromycin	≤0.25	>2	0.25 – >2	58.3	4.2
Clindamycin	≤0.25	>2	0.25 – >2	95.8	–
Linezolid	0.5	1	0.25 – 1	100.0	8.3
Quinupristin-dalfopristin	0.5	1	0.25 – 2	91.7	20.8
Tetracycline	≤2	>8	2 – >8	79.2	–
Trimethoprim-sulfamethoxazole	≤0.5	>2	0.5 – >2	–	–
Vancomycin	≤1	0.5	≤1 – 0.5	100.0	–
β-hemolytic streptococci (77)					
Ceftobiprole	≤0.06	<0.06	≤0.06	–	–
Penicillin	≤0.016	0.06	≤0.016 – 0.12	100.0	–
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	–
Levofloxacin	≤0.5	1	≤0.5 – 1	100.0	0.0
Erythromycin	≤0.25	≤0.25	≤0.25	94.8	5.2
Clindamycin	≤0.25	≤0.25	≤0.25	100.0	0.0
Linezolid	0.5	1	0.5 – 1	100.0	–
Quinupristin-dalfopristin	≤0.25	≤0.25	≤0.25 – 0.5	100.0	0.0
Tetracycline	≤2	>8	≤2 – >8	58.4	41.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5	–	–
Vancomycin	0.25	0.5	0.25 – 0.5	100.0	–

[a]Susceptibility breakpoint criteria of the CLSI (2006); no breakpoints have been assigned to ceftobiprole. [b]Percentage nonsusceptible (intermediate and resistant). [c]Meningitis breakpoints as specified by CLSI [2006].

Table 2. Antimicrobial activity of ceftobiprole tested against *S. aureus*, CoNS, and streptococci, including resistant subsets, recovered from patients in Latin American medical centers (2005)

	MIC (µg/ml)		Cumulative % inhibited at MIC (µg/ml)					
Organism (no. tested)	50%	90%	≤0.12	0.25	0.5	1	2	4
S. aureus								
Oxacillin-susceptible (363)	0.25	0.5	2	61	>99	>99	100	–
Oxacillin-resistant (147)	2	2	0	<1	7	30	96	100
CoNS								
Oxacillin-susceptible (40)	0.12	0.25	50	100	–	–	–	–
Oxacillin-resistant (143)	1	2	3	12	34	66	92	98
S. pneumoniae								
Penicillin-susceptible (211)	≤0.06	≤0.06	100	–	–	–	–	–
Penicillin-resistant (43)	0.25	0.5	7	63	100	–	–	–
Viridans group streptococci (24)	≤0.06	0.25	87	92	100	–	–	–
β-hemolytic streptococci (77)	≤0.06	≤0.06	100	–	–	–	–	–

Results

- Ceftobiprole inhibited all tested Latin American origin staphylococci at 4 µg/ml, with the exception of 3 *S. haemolyticus* isolates with a ceftobiprole MIC of 8 µg/ml.
- All streptococci were inhibited at a ceftobiprole MIC of 0.5 µg/ml (**Table 1**).
- While ceftobiprole MIC_{90} values for oxacillin-resistant strains were 4- and 8-fold higher for *S. aureus* and CoNS, respectively, published pharmacokinetic/pharmacodynamic characteristics suggest that target attainment for both oxacillin-susceptible and -resistant populations is achievable (**Table 2**).
- Oxacillin resistance in Latin American *S. aureus* was 28.8%, similar to that seen in Europe (25.9%) and lower than is recognized for North America (USA; 49.8%). Oxacillin resistance among CoNS was similar for all regions (69.6-78.1%; data not shown).
- Ceftobiprole potency against oxacillin-susceptible and -resistant *S. aureus* from North America was nearly identical to those presented here ($MIC_{50/90,}$ 0.25/0.5 and 1/2 µg/ml, respectively; data not shown).
- Vancomycin, linezolid, and daptomycin retained full susceptibility against all tested staphylococci from Latin America (**Table 1**).
- All strains of *S. pneumoniae* were inhibited by 0.5 µg/ml of ceftobiprole despite the increased rates of penicillin-and ceftriaxone-nonsusceptibility (31.7 and 11.3%). Ceftobiprole and ceftriaxone were 4- to 8-fold more potent against penicillin-susceptible strains compared with penicillin-resistant strains.
- Vancomycin, linezolid, quinupristin-dalfopristin, and levofloxacin also provided excellent activity against *S. pneumoniae* (**Table 1**).
- Ceftobiprole and penicillin were the most active agents tested against β-hemolytic streptococci (MIC_{90} values ≤0.06 and 0.06 µg/ml, respectively) and viridans group streptococci (0.25 and 0.5 µg/ml). All strains were inhibited by 0.5 µg/ml of ceftobiprole.

Conclusions

- **Among Gram-positive bacterial pathogens recovered from Latin American medical centers in 2005, ceftobiprole inhibited all streptococci at 0.5 µg/ml and all staphylococci at 4 µg/ml with the exception of 3 strains of *S. haemolyticus* at 8 µg/ml.**
- **While potency of ceftobiprole against resistant subsets is decreased (2- to 8-fold for oxacillin-resistant staphylococci and penicillin-resistant pneumococci), >99% of strains may be expected to be inhibited at achievable *in-vivo* concentrations.**
- **Ceftobiprole displays potent activity against those staphylococci and streptococci responsible for skin and skin-structure infections, and community-associated respiratory infections, respectively, in Latin America and is unique in retaining activity against pathogens routinely resistant to other β-lactam antimicrobics.**

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