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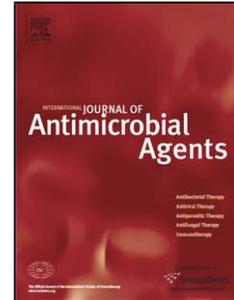
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Comparative in vitro activity of ceftobiprole against Gram-positive cocci [☆]

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ABSTRACT

The activity of ceftobiprole and comparator agents was evaluated against a collection of 880 isolates, comprising 200 meticillin-susceptible *Staphylococcus aureus*, 200 meticillin-resistant *S. aureus*, 180 coagulase-negative staphylococci blood isolates, 100 *Streptococcus pneumoniae* and 200 macrolide-resistant β -haemolytic streptococci (100 *Streptococcus pyogenes* and 100 *Streptococcus agalactiae*). Ceftobiprole showed excellent activity against staphylococci (minimum inhibitory concentrations $\leq 4 \mu\text{g/mL}$), irrespective of their susceptibility to other agents such as oxacillin, linezolid or glycopeptides. Ceftobiprole was also highly active against penicillin-resistant *S. pneumoniae* and macrolide-resistant β -haemolytic streptococci, inhibiting 99.6% of all streptococci tested at $\leq 0.5 \mu\text{g/mL}$. Based on these results, ceftobiprole appears to be a promising agent for the treatment of infections caused by multidrug-resistant Gram-positive pathogens.

1. Introduction

The rising incidence of infections caused by multidrug-resistant Gram-positive bacteria, such as methicillin-resistant staphylococci or penicillin-resistant pneumococci, underscores the need for novel agents with activity against these pathogens. Ceftobiprole is an expanded-spectrum pyrrolidinone-3-ylidene-methyl cephalosporin with documented in vitro activity against a wide range of Gram-positive cocci, including methicillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae*. Ceftobiprole is also active against Gram-negative bacilli, including *Pseudomonas aeruginosa*. It is active against methicillin-resistant *Staphylococcus aureus* (MRSA) because of its high affinity for penicillin-binding protein 2a (PBP2a) and its stability against class A β -lactamases. It also binds to PBP2X, which mediates penicillin resistance in *S. pneumoniae*. The bactericidal activity of ceftobiprole against MRSA has been demonstrated by several authors [1–3]. Ceftobiprole has been reported to have low potential for selection of resistance in multiple-passage studies [4,5].

The objective of this study was to assess the activity of ceftobiprole and several comparator agents against a variety of Gram-positive cocci.

2. Materials and methods

The activity of ceftobiprole and comparator agents was analysed against a collection of 880 isolates, comprising 200 methicillin-susceptible *S. aureus* (MSSA), 200 MRSA, 180 coagulase-negative staphylococci (CoNS) blood isolates, 100 *S. pneumoniae* and 200 macrolide-resistant β -haemolytic

streptococci (100 *Streptococcus pyogenes* and 100 *Streptococcus agalactiae*). The sources of the isolates were blood (77.5%), respiratory tract (11.2%), skin and soft-tissues (6.5%), urine (2.9%), genital tract (1.2%) and abdominal tract (0.6%). Organisms were identified by standard methods including latex agglutination (Slidex Staph, Slidex Pneumo, Slidex Strepto A and Slidex Strepto B Kits; bioMérieux, Marcy l'Etoile, France). CoNS were identified using the Vitek 2 Gram-positive identification card (bioMérieux) and species were distributed as follows: 113 *Staphylococcus epidermidis*; 42 *Staphylococcus hominis*; 20 *Staphylococcus haemolyticus*; 3 *Staphylococcus lugdunensis*; 1 *Staphylococcus intermedius*; and 1 *Staphylococcus warneri*. The quality control strains *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 were included in each testing run.

Antimicrobial susceptibility testing was performed using the reference broth microdilution method described by the Clinical and Laboratory Standards Institute (CLSI) [6]. Cation-adjusted Mueller–Hinton broth was supplemented with 5% lysed horse blood for streptococci. A calcium supplement (up to 50 µg/mL) was used for testing daptomycin. Sensititre microdilution panels (Trek Diagnostic Systems, East Grinstead, UK) were used for all the drugs except ceftobiprole. The microdilution trays for ceftobiprole were prepared in house using fresh broth and following the recommendations of the CLSI [6]. Ceftobiprole standard powder was provided by Johnson & Johnson Pharmaceutical Research and Development (Raritan, NJ). Stock solution of ceftobiprole was prepared and dissolved according to the CLSI method [7]. The

group of antimicrobial agents tested varied according to the bacterial species and are listed in Table 1.

3. Results

The activities of ceftobiprole and comparator agents against all staphylococci and streptococci tested are shown in Table 1. Based on the MIC₅₀/MIC₉₀ values (minimum inhibitory concentrations for 50% and 90% of the organisms, respectively), the activity of ceftobiprole (0.5/1 µg/mL) against all *S. aureus* tested was comparable with that of vancomycin (1/1 µg/mL), teicoplanin (0.5/1 µg/mL) and daptomycin (0.25/0.5 µg/mL). Six MRSA isolates were resistant to linezolid (MICs ≥ 8 µg/mL) and one MRSA isolate showed intermediate susceptibility to vancomycin (MIC = 4 µg/L). Among CoNS, three isolates were resistant to linezolid and four were resistant to teicoplanin (MICs ≥ 32 µg/mL). Daptomycin was active against all the staphylococci tested. Ceftobiprole MICs were ≤4 µg/mL against all staphylococci, with MIC₅₀ and MIC₉₀ values four-fold lower for MSSA isolates than for MRSA isolates.

According to the CLSI cefotaxime breakpoints for non-meningeal isolates [7], 14% of the *S. pneumoniae* isolates tested were not susceptible to cefotaxime (MICs ≥ 2 µg/mL). All of these isolates were inhibited by ceftobiprole at MICs of ≤1 µg/mL. For macrolide-resistant *S. pyogenes*, resistance rates to clindamycin and tetracycline were 10% and 14%, respectively. The MIC₅₀ and MIC₉₀ values for ceftobiprole were ≤0.008 µg/mL and 0.015 µg/mL, respectively. More than one-half (54%) of the macrolide-resistant *S. agalactiae* were resistant to

clindamycin and 84% were resistant to tetracycline. Among the 100 macrolide-resistant *S. agalactiae* isolates, the MIC₅₀ and MIC₉₀ values for ceftobiprole were 0.015 µg/mL and 0.03 µg/mL, respectively.

Table 2 presents the distribution of ceftobiprole MICs for each group of organisms tested. The percentages of *S. pneumoniae* isolates inhibited at 0.25 µg/mL and 0.5 µg/mL ceftobiprole were 94% and 99%, respectively. The *S. pyogenes* and *S. agalactiae* isolates tested were inhibited at ≤0.015 µg/mL and ≤0.25 µg/mL, respectively. Among staphylococci, meticillin-susceptible isolates were more susceptible to ceftobiprole than meticillin-resistant isolates (Table 2). CLSI interpretative breakpoints are not yet available for ceftobiprole. By applying the ceftobiprole susceptibility breakpoint interpretations used in a previous study [8] (MIC ≤4 µg/mL for staphylococci and MIC ≤1 µg/mL for streptococci), all the isolates included in the present study were susceptible to ceftobiprole.

4. Discussion

Unlike other studies [2,4,9] in which the staphylococci tested were all susceptible to linezolid, the present study included some staphylococcal isolates that were not susceptible to this antibiotic. Ceftobiprole showed excellent activity against staphylococci irrespective of their susceptibility to other agents such as oxacillin, linezolid or glycopeptides. Our results are similar to those previously reported by Fritsche et al. [10]. Ceftobiprole was also highly active against penicillin-resistant *S. pneumoniae* and macrolide-resistant β-

haemolytic streptococci, inhibiting 99.7% of all streptococci tested at ≤ 0.5 $\mu\text{g/mL}$. In agreement with the data reported by Jones et al. [8], all pneumococci were inhibited by ceftobiprole at MICs ≤ 1 $\mu\text{g/mL}$. Ceftobiprole MIC₅₀ and MIC₉₀ values against *S. pneumoniae* (≤ 0.008 $\mu\text{g/mL}$ and 0.25 $\mu\text{g/mL}$ respectively) were similar to those reported by Pillar et al. [9]. To our knowledge, only three published studies [8,10,11] have reported ceftobiprole activity against β -haemolytic streptococci. Two of them [8,10] presented results for these organisms as a group without differentiating between species. In the third study [11], as in ours, the results for *S. pyogenes* and *S. agalactiae* are presented separately. However, the authors studied a smaller number of isolates ($n = 71$ and $n = 42$, respectively) than we did and included macrolide-susceptible and -resistant isolates. We found that ceftobiprole was slightly more active against erythromycin-resistant *S. pyogenes* isolates than against erythromycin-resistant *S. agalactiae* isolates. This new cephalosporin inhibited 100% of *S. pyogenes* and *S. agalactiae* isolates tested at 0.015 $\mu\text{g/mL}$ and 0.25 $\mu\text{g/mL}$, respectively.

Based on our findings and those of other authors [8–12], together with the drug's excellent pharmacokinetic and safety profiles [13,14], ceftobiprole appears to be a promising agent for the treatment of infections caused by multidrug-resistant Gram-positive pathogens.

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Competing interests

None declared.

Ethical approval

Not required.

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Table 1

In vitro activity of ceftobiprole and comparator agents against staphylococci and streptococci

Organism (no. of isolates)/antimicrobial agent	MIC ($\mu\text{g/mL}$)		
	Range	MIC ₅₀	MIC ₉₀
<i>Staphylococcus aureus</i> oxacillin-susceptible ($n = 200$)			
Ceftobiprole	0.125–0.5	0.25	0.5
Daptomycin	≤ 0.125 –1	0.25	0.5
Linezolid	≤ 0.25 –4	1	2
Vancomycin	≤ 0.5 –2	1	1
Teicoplanin	≤ 0.5 –2	0.5	1
<i>S. aureus</i> oxacillin-resistant ($n = 200$)			
Ceftobiprole	0.25–4	1	2
Daptomycin	≤ 0.125 –1	0.5	0.5
Linezolid	≤ 0.25 to >8	2	2
Vancomycin	≤ 0.5 –4	1	2
Teicoplanin	≤ 0.5 –4	≤ 0.5	1
CoNS oxacillin-susceptible ($n = 39$)			
Ceftobiprole	0.06–1	0.125	0.25
Daptomycin	≤ 0.125 –0.5	0.25	0.5
Linezolid	≤ 0.25 –2	1	2
Vancomycin	≤ 0.5 –2	2	2
Teicoplanin	≤ 0.5 –8	2	4
CoNS oxacillin-resistant ($n = 141$)			
Ceftobiprole	0.125–4	1	2
Daptomycin	≤ 0.125 –1	0.25	0.5
Linezolid	0.5 to >8	1	2
Vancomycin	≤ 0.5 –4	2	2
Teicoplanin	≤ 0.5 –32	2	8
<i>Streptococcus pneumoniae</i> ($n = 100$)			
Ceftobiprole	≤ 0.008 –1	≤ 0.008	0.25
Cefotaxime	≤ 0.06 –4	≤ 0.06	2

Penicillin	≤0.03–4	≤0.03	2
Levofloxacin	≤0.5–2	1	2
Vancomycin	≤0.25–1	0.5	0.5
<i>Streptococcus pyogenes</i> erythromycin-resistant (<i>n</i> = 100)			
Ceftobiprole	≤0.008–0.015	≤0.008	0.015
Penicillin	≤0.03	≤0.03	≤0.03
Clindamycin	≤0.25 to >0.5	≤0.25	>0.5
Telithromycin	≤0.06–16	0.25	0.5
Tetracycline	≤2 to >4	≤2	>4
<i>Streptococcus agalactiae</i> erythromycin-resistant (<i>n</i> = 100)			
Ceftobiprole	≤0.008–0.25	0.015	0.03
Penicillin	≤0.03–0.06	≤0.03	≤0.03
Clindamycin	≤0.25 to >0.5	>0.5	>0.5
Telithromycin	≤0.06–8	≤0.06	0.5
Tetracycline	≤2 to >4	>4	>4

MIC, minimum inhibitory concentration; MIC_{50/90}, MIC for 50% and 90% of the organisms, respectively; CoNS, coagulase-negative staphylococci.

Table 2

Distribution of ceftobiprole minimum inhibitory concentrations (MICs)

Organism (no. tested)	Cumulative % inhibited at MIC ($\mu\text{g/mL}$)									
	≤ 0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
<i>Staphylococcus aureus</i> oxacillin-susceptible ($n = 200$)					1.5	60.5	100			
<i>S. aureus</i> oxacillin-resistant ($n = 200$)						1	20.5	88	96	100
CoNS oxacillin-susceptible ($n = 39$)				5.1	71.8	94.9	94.9	100		
CoNS oxacillin-resistant ($n = 141$)					0.7	12.1	29.8	73.8	95.7	100
<i>Streptococcus pneumoniae</i> ($n = 100$)	59	66	71	72	75	94	99	100		
<i>Streptococcus pyogenes</i> erythromycin-resistant ($n = 100$)	60	100								
<i>Streptococcus agalactiae</i> erythromycin-resistant ($n = 100$)	21	69	89	96	98	100				

MIC, minimum inhibitory concentration; CoNS, coagulase-negative staphylococci.