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In vitro pharmacodynamics of ceftobiprole against Staphylococcus aureus at concentrations corresponding to free drug levels achieved in human serum

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Background: Ceftobiprole is a cephalosporin with a broad-spectrum of activity. Ceftobiprole is active against Gram-positive and Gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* and is known to exert bactericidal activity. The objective of this study was to investigate the *in vitro* activity of ceftobiprole, in comparison to cefuroxime, flucloxacillin, linezolid and vancomycin, against four methicillin-susceptible *S. aureus* (MSSA) and seven MRSA strains by time-kill methodology. Concentrations used were those corresponding to human peak free serum conc. (fC_{max}) as well as concentrations corresponding to the free-drug concentrations achieved for 40–50% of the dosing interval.

Material/methods: Minimum inhibitory concentrations (MIC) were determined by the broth microdilution procedure. Time-kill assays were performed in glass flasks containing 20 mL of cation-adjusted Mueller-Hinton-broth, at starting inocula of approximately 5×10^5 colony-forming units (CFU)/mL (low inoculum) or 5×10^7 CFU/mL (high inoculum). Final concentrations were 25 / 12 mg/L for ceftobiprole, 80 / 10 mg/L for cefuroxime, 12 / 1.5 mg/L for flucloxacillin, 10 / 5 mg/L for linezolid, and 30 / 15 mg/L for vancomycin, consistent with the following dosing regimens: ceftobiprole medocaril 500 mg i.v. over 2 h t.i.d., cefuroxime at 1,500 mg i.v. over 30 min t.i.d., flucloxacillin 2,000 mg i.v. over 30 min q.i.d., linezolid at 600 mg i.v. over 1 h b.i.d, and vancomycin 1,000 mg i.v. over 1 h b.i.d. Ceftobiprole was tested against all strains (4 MSSA, 7 MRSA), cefuroxime and flucloxacillin against three MSSA strains, and linezolid and vancomycin against one linezolid-resistant MSSA and all MRSA strains (Table). All experiments were performed in duplicate.

Results: With both inocula, ceftobiprole demonstrated comparable killing activity to cefuroxime and flucloxacillin (MSSA) and vancomycin (MRSA). Ceftobiprole had a more rapid killing effect than

vancomycin within the first 6 h against the strains MU3 (hVISA) and MU50 (VISA), while in contrast, vancomycin had a more rapid killing effect than ceftobiprole against MRSA strains CR-15-18 and PEG-10-62-55 (USA300). As expected, linezolid exerted a bacteriostatic effect against any strain. The killing activity of ceftobiprole was not improved at the higher tested concentration. Changes in viable counts, determined 24 h after exposure to ceftobiprole, flucloxacillin or vancomycin, are displayed in the Table.

Table: Changes in viable counts (log_{10} CFU/mL) at 24 h

Organism (Characteristics)	MIC (mg/L) BPR / FLU or VAN#	BPR *f*Cmax / *f*C4h 25 / 12 mg/L	FLU *f*Cmax / *f*C4h 12 / 1.5 mg/L	VAN *f*Cmax / *f*C6h 30 / 15 mg/L
ATCC 29213 (MSSA)	L: 0.25 / 0.125-0.25 H: 0.5 / 0.25-0.5	L: -3.3 / -3.4 H: -2.2 / -2.4	L: -3.3 / -2.7 H: -2.7 / -2.8	-
ATCC 25923 (MSSA)	L: 0.25 / 0.125 H: 0.5 / 0.5	L: -3.0 / -2.9 H: -2.9 / -2.8	L: -2.7 / -2.4 H: -2.6 / -2.7	-
CR-2-33 (MSSA, blood isolate)	L: 0.5 / 0.25 H: 0.5-1 / 0.5	L: -3.9 / -3.8 H: -3.8 / -3.7	L: -4.1 / -3.6 H: -5.6 / -4.3	-
710-5-68 (MSSA, porcine isolate, LZD-resistant)	L: 0.25 / 0.5 H: 0.5 / 2	L: -2.7 / -3.5 H: -3.9 / -5.1	-	L: -4.1 / -4.1 H: -4.3 / -3.7
CR-5-81 (MRSA, blood isolate, spa t003)	L: 2 / 1-2 H: 2-4 / 2-4	L: -3.4 / -3.7 H: -2.2 / -3.0	-	L: -4.3* / -4.4* H: -3.1 / -3.2
CR-15-18 (MRSA, blood isolate, spa t032)	L: 1 / 1 H: 2 / 2-4	L: -2.1 / -2.7 H: -2.0 / -2.7	-	L: -4.5* / -4.5* H: -4.8 / -4.0
PEG-10-51-3 (MRSA, throat swab isolate, spa t001)	L: 4 / 1 H: 4-8 / 2-4	L: -3.9 / -3.7 H: -2.7 / -3.7	-	L: -4.3* / -3.8 H: -3.6 / -3.7
PEG-10-62-55 (MRSA, USA300, spa t008)	L: 1 / 1 H: 2 / 2	L: -2.3 / -2.0 H: -1.3 / -1.7	-	L: -4.4* / -4.4* H: -3.2 / -3.2
42080 (MRSA, VAN-S, TPL-R)	L: 2 / 2 H: 4 / 4-8	L: -2.8 / -2.9 H: -2.1 / -2.7	-	L: -4.1* / -3.9 H: -2.5 / -2.4
Mu50 (MRSA, VISA)	L: 2 / 8 H: 4 / 16	L: -4.3 / -4.0 H: -4.0 / -4.6	-	L: -3.8 / -3.8 H: -3.6 / -2.2
Mu3 (MRSA, hVISA)	L: 2 / 2-4 H: 4 / 4-8	L: -3.9 / -4.3 H: -3.1 / -3.9	-	L: -4.5* / -4.5* H: -3.3 / -3.4

Abbreviations: BPR, ceftobiprole; FLU, flucloxacillin; VAN, vancomycin; LZD, linezolid; TPL, teicoplanin; S, susceptible; R, resistant; L, low inoculum; H, high inoculum; *below the limit of detection
#Underlined values represent MIC values of FLU; not underlined values represent MIC values of VAN

Conclusions: At clinically-achievable levels, ceftobiprole produced kill kinetics typical for β-lactams against *S. aureus*, resulted in adequate killing effects against both MSSA and MRSA, and exerted a more potent early-bactericidal effect than vancomycin against the hVISA strain and the VISA strain.