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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 group 5 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 (1–3).

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 according to ISO 20776-1 (4). Test strains were classified as *susceptible*, *intermediate* or *resistant* by using the clinical breakpoints set by EUCAST (5). 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 500 mg i.v. over 2 h t.i.d. (6), cefuroxime at 1,500 mg i.v. over 30 min t.i.d. (7), flucloxacillin 2,000 mg i.v. over 30 min q.i.d. (8), linezolid at 600 mg i.v. over 1 h b.i.d. (9), and vancomycin 1,000 mg i.v. over 1 h b.i.d. (10). 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. All experiments were performed in duplicate.

Results

Results are presented in the tables.

Conclusions

At clinically-achievable levels, ceftobiprole produced kill kinetics typical for β-lactams against *S. aureus*, resulted in 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.

References

1. Amsler KM et al. 2008. Antimicrob Agents Chemother. 52: 3418-3423.
2. Farrell DJ et al. 2014. Antimicrob Agents Chemother. 58: 3882-3888.
3. Walkty A et al. 2008. J Antimicrob Chemother. 62: 206–208.
4. ISO 20776-1: 2006. German version EN ISO 20776-1:2006. Beuth-Verlag, Berlin.
5. European Committee on Antimicrobial Susceptibility Testing (EUCAST). 2016. Breakpoint tables v 6.0.
6. Summary of product characteristics - ZEVTERA 500 mg powder for concentrate for solution for infusion.
7. Fachinformation Zinacef® Hikma 1500 mg.
8. Fachinformation Fluclox Stragen 1 g/- 2 g.
9. Fachinformation Zyvoxid® 100 mg/5 ml.
10. Fachinformation Vancomycin „Lederle“ 1000 mg.

Disclosures

MK is a partner and CEO of Antiinfectives Intelligence GmbH, a research organization providing services to pharmaceutical companies. BK-I is head of laboratory of Antiinfectives Intelligence GmbH.

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Table 1: Susceptibility of test strains

MSSA Strain no. (characteristics)	Inoculum	MIC (mg/L)*		
		BPR	CXM	FLU
ATCC 29213	Low	0.25	1	0.125-0.25
	High	0.5	1	0.25-0.5
ATCC 25923	Low	0.25	0.5	0.125
	High	0.5	1	0.5
CR-2-33 (BC)	Low	0.5	1-2	0.25
	High	0.5-1	1	0.5
MSSA Strain no. (characteristics)	**Inoculum**	**MIC (mg/L)***		
		BPR	**LZD**	**VAN**
710-5-68 (PI, LZD-R)	Low	0.25	4-8	0.5
	High	0.5	8-16	2

MRSA Strain no. (characteristics)	Inoculum	MIC (mg/L)*		
		BPR	LZD	VAN
CR-5-81 (BC, t003)	Low	2	1-2	1-2
	High	2-4	8	2-4
CR-15-18 (BC, t032)	Low	1	2	1
	High	2	4-8	2-4
PEG-10-51-3 (TS, t001)	Low	4	2-4	1
	High	4-8	8	2-4
PEG-10-62-55 (W, t008)	Low	1	1-2	1
	High	2	8	2
42080 (VAN-S, TPL-R)	Low	2	1	2
	High	4	4-8	4-8
MU3 (hVISA)	Low	2	1-2	2-4
	High	4	4	4-8
MU50 (VISA)	Low	2	1	8
	High	4	4	16

Abbrevations: BPR, ceftobiprole; CXM, cefuroxime; FLU, flucloxacillin; LZD, linezolid; TPL, teicoplanin; VAN, vancomycin; S, susceptible; R, resistant; BC, blood culture isolate; TS, throat swab isolate; PI, porcine isolate; W, wound isolate; VISA, vancomycin-intermediate *Staphylococcus aureus*
*MICs were determined twice.

Table 2: Change in viable counts of MSSA strains

Strain no.	Drug	Dosing regiment (conc. mg/L)	Low inoculum Difference (log10 CFU/mL)		High inoculum Difference (log10 CFU/mL)	
			at 6 h	at 24 h	at 6 h	at 24 h
ATCC 29213	BPR	fC_{4h} (12)	-0.73	**-3.43**	-0.54	-2.35
		fC_{max} (25)	-0.99	**-3.29**	-0.69	-2.18
	CXM	fC_{4h} (10)	-0.83	-2.78	-0.81	-2.59
		fC_{max} (80)	-0.87	**-4.01**	-0.96	-2.63
	FLU	fC_{4h} (1.5)	-1.08	-2.74	-1.37	-2.76
		fC_{max} (12)	-1.40	**-3.29**	-1.76	-2.67
ATCC 25923	BPR	fC_{4h} (12)	-0.75	-2.89	-0.75	-2.79
		fC_{max} (25)	-1.00	**-3.00**	-0.77	-2.88
	CXM	fC_{4h} (10)	-0.79	**-3.13**	-0.70	-1.98
		fC_{max} (80)	-0.97	**-4.03**	-0.96	-2.67
	FLU	fC_{4h} (1.5)	-1.06	-2.42	-1.12	-2.74
		fC_{max} (12)	-1.11	-2.65	-0.99	-2.55
CR-2-33	BPR	fC_{4h} (12)	-1.73	**-3.82**	-1.63	**-3.72**
		fC_{max} (25)	-2.11	**-3.87**	-1.58	**-3.79**
	CXM	fC_{4h} (10)	-2.67	**-3.76**	-1.68	**-4.60**
		fC_{max} (80)	**-3.45**	**-4.26***	-1.98	**-4.72**
	FLU	fC_{4h} (1.5)	-2.72	**-3.63**	-2.46	**-4.26**
		fC_{max} (12)	**-3.27**	**-4.14**	-2.59	**-5.62**
710-5-68	BPR	fC_{4h} (12)	-0.48	**-3.53**	-1,08	**-5.11**
		fC_{max} (25)	-0.58	-2.65	-0.78	**-3.91**
	LZD	fC_{6h} (5)	0.37	2.87	0.63	1.80
		fC_{max} (10)	0.13	2.02	0.24	1.47
	VAN	fC_{6h} (15)	-0.78	**-4.10**	-1.15	**-3.74**
		fC_{max} (30)	-0.83	**-4.08**	-1.00	**-4.25**

Abbreviations: BPR, ceftobiprole; CXM, cefuroxime; FLU, flucloxacillin; LZD, linezolid; VAN, vancomycin; conc., concentration
*below limit of detection (<20 CFU/mL); numbers in bold indicate a bactericidal effect

Table 3: Change in viable counts of MRSA strains

Strain no.	Drug	Dosing regiment (conc. mg/L)	Low inoculum Difference (log10 CFU/mL)		High inoculum Difference (log10 CFU/mL)	
			at 6 h	at 24 h	at 6 h	at 24 h
CR-5-81	BPR	fC_{4h} (12)	-0.50	**-3.74**	-0.39	-2.95
		fC_{max} (25)	-0.65	**-3.36**	-0.17	-2.18
	LZD	fC_{6h} (5)	-0.06	-0.72	-0.05	-0.01
		fC_{max} (10)	-0.16	-1.47	-0.14	-1.05
	VAN	fC_{6h} (15)	-0.84	**-4.41***	-0.58	**-3.21**
		fC_{max} (30)	-0.80	**-4.33***	-0.70	**-3.07**
CR-15-18	BPR	fC_{4h} (12)	-0.82	-2.73	-0.66	-2.69
		fC_{max} (25)	-0.62	-2.10	-0.44	-1.95
	LZD	fC_{6h} (5)	-0.20	-1.19	-0.18	-0.01
		fC_{max} (10)	-0.12	1.40	-0.15	-0.50
	VAN	fC_{6h} (15)	-1.31	**-4.49***	-0.64	**-3.95**
		fC_{max} (30)	-1.38	**-4.47***	-0.84	**-4.79**
PEG-10-51-3	BPR	fC_{4h} (12)	-1.35	**-3.67**	-1.15	**-3.68**
		fC_{max} (25)	-1.26	**-3.88**	-0.64	-2.71
	LZD	fC_{6h} (5)	-0.18	0.59	-0.12	0.32
		fC_{max} (10)	-0.11	-0.78	-0.39	-0.49
	VAN	fC_{6h} (15)	-1.01	**-3.76**	-0.84	**-3.72**
		fC_{max} (30)	-1.08	**-4.28***	-0.88	**-3.57**
PEG-10-62-55	BPR	fC_{4h} (12)	-0.81	-1.94	-0.71	-1.66
		fC_{max} (25)	-0.79	-2.27	-0.61	-1.26
	LZD	fC_{6h} (5)	-0.16	-1.07	-0.07	0.24
		fC_{max} (10)	-0.23	-1.23	-0.28	-0.77
	VAN	fC_{6h} (15)	-0.99	**-4.42***	-0.85	**-3.20**
		fC_{max} (30)	-1.01	**-4.35***	-0.86	**-3.21**
42080	BPR	fC_{4h} (12)	-0.82	-2.94	-0.73	-2.74
		fC_{max} (25)	-1.00	-2.79	-0.52	-2.12
	LZD	fC_{6h} (5)	-0.78	-2.32	-0.46	-1.87
		fC_{max} (10)	-1.21	-2.51	-0.56	-1.95
	VAN	fC_{6h} (15)	-0.66	**-3.86**	-0.51	-2.42
		fC_{max} (30)	-0.86	**-4.13***	-0.45	-2.48
MU3	BPR	fC_{4h} (12)	-2.69	**-4.27**	-2.32	**-3.91**
		fC_{max} (25)	-2.81	**-3.91**	-1.72	**-3.11**
	LZD	fC_{6h} (5)	-0.32	-1.84	-0.15	-1.72
		fC_{max} (10)	-0.59	-1.65	-0.66	-1.99
	VAN	fC_{6h} (15)	-1.18	**-4.49***	-0.86	**-3.35**
		fC_{max} (30)	-1.49	**-4.45***	-0.92	**-3.27**
MU50	BPR	fC_{4h} (12)	-1.90	**-4.03**	-2.11	**-4.60**
		fC_{max} (25)	-2.01	**-4.31**	-1.94	**-3.97**
	LZD	fC_{6h} (5)	-0.92	-2.44	-1.00	-1.86
		fC_{max} (10)	-1.09	-2.60	-1.27	-2.22
	VAN	fC_{6h} (15)	-0.63	**-3.75**	-0.54	-2.23
		fC_{max} (30)	-0.66	**-3.82**	-0.69	**-3.56**

Abbreviations: BPR, ceftobiprole; LZD, linezolid; VAN, vancomycin; conc., concentration
*below limit of detection (<20 CFU/mL); numbers in bold indicate a bactericidal effect