

In vitro activity of ceftaroline against *Staphylococcus aureus* using concentrations achieved in humans determined by time-kill methodology

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Introduction and Purpose

Ceftaroline (CPT) fosamil is known to exert bactericidal activity against MRSA, but published data on the in vitro activity tested by time-kill assay is scarce.

The objective of this study was to investigate the in vitro activity of CPT, in comparison to flucloxacillin (FLU) and vancomycin (VAN), against two methicillin-susceptible *S. aureus* (MSSA) and six methicillin-resistant *S. aureus* (MRSA) by time-kill methodology.

Methods

Time-kill assays were performed in 20 mL of cation-adjusted Mueller-Hinton-broth. Two starting inocula were applied – 5×10^5 CFU/mL (low inoculum) and 5×10^7 CFU/mL (high inoculum).

Drug concentrations (conc.) corresponded to human peak free serum conc. (fC_{max}) as well as to the free-drug conc. achieved for 40-50% of the dosing interval (16 / 6 / 4 mg/L for CPT, 12 / 1.5 mg/L for FLU, 30 / 15 mg/L for VAN) based on the following dosing regimens: CPT fosamil 600 mg iv over 1 h every 12 h, CPT fosamil at 600 mg iv over 1 h every 8 h, FLU 2,000 mg iv over 30 min every 6 h, and vancomycin 1,000 mg iv over 1 h every 12 h.

Results

Results are presented in the tables.

Conclusions

- CPT at clinically achievable levels showed kill kinetics typical for β -lactams against *S. aureus* resulting in adequate killing effects against both MSSA and MRSA.
- CPT exerted a more potent early bactericidal effect than VAN against MRSA.

Table 1: Susceptibility of test strains

Strain no.	Inoculum	MIC (mg/L)*		
		CPT	FLU	VAN
ATCC 29213 (MSSA)	Low	0.25	0.25	
	High	0.5-1	0.25-0.5	
CR-2-33 (BC, MSSA)	Low	0.25	0.25	
	High	0.25	0.5	
CR-5-81 (BC, t003, MRSA)	Low	0.5		1
	High	1		2
CR-15-18 (BC, t032, MRSA)	Low	1		1
	High	1		2
710-5-53 (BC, t1068, MRSA)	Low	2		0.5
	High	2		2
PEG-10-62-55 (W, t008, MRSA)	Low	0.5-1		0.5
	High	1-2		2
MU3 (hetero-VISA)	Low	1		2-4
	High	2		4
MU50 (VISA)	Low	1		4-8
	High	2		8-16

Abbreviations: CPT, ceftaroline; FLU, flucloxacillin; VAN, vancomycin; BC, blood culture isolate; W, wound isolate; VISA, vancomycin-intermediate *S. aureus*

*MICs were determined twice.

Table 2: Change in viable counts of MSSA strains

Strain no.	Drug	Dosing regiment (conc. mg/L)	Low inoculum		High inoculum	
			$\Delta \log$ CFU/mL at 6 h	$\Delta \log$ CFU/mL at 24 h	$\Delta \log$ CFU/mL at 6 h	$\Delta \log$ CFU/mL at 24 h
ATCC 29213 (MSSA)	CPT	fC_{6h} (4)	-0.96	-3.46	-1.31	-2.26
		fC_{4h} (6)	-1.11	-3.31	-1.33	-2.41
		fC_{max} (16)	-1.42	-4.13	-1.50	-2.58
	FLU	fC_{4h} (1.5)	-0.85	-2.59	-0.97	-2.48
		fC_{max} (12)	-1.86	-3.18	-2.18	-2.83
CR-2-33 (MSSA)	CPT	fC_{6h} (4)	-3.70	-4.24*	-2.32	-6.05
		fC_{4h} (6)	-3.83	-4.26*	-2.64	-6.08
		fC_{max} (16)	-3.96	-4.20*	-2.62	-6.12
	FLU	fC_{4h} (1.5)	-2.89	-3.53	-2.24	-4.57
		fC_{max} (12)	-3.62	-4.21*	-2.72	-6.08

Abbreviations: CPT, ceftaroline; FLU, flucloxacillin; 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		High inoculum	
			$\Delta \log$ CFU/mL at 6 h	$\Delta \log$ CFU/mL at 24 h	$\Delta \log$ CFU/mL at 6 h	$\Delta \log$ CFU/mL at 24 h
CR-5-81 (MRSA)	CPT	fC_{6h} (4)	-1.01	-4.17*	-0.94	-2.77
		fC_{4h} (6)	-1.32	-4.18*	-0.97	-2.75
		fC_{max} (16)	-1.34	-4.18*	-0.97	-3.28
	VAN	fC_{6h} (15)	-0.62	-4.18*	-0.55	-2.93
		fC_{max} (30)	-0.79	-4.20*	-0.49	-3.01
CR-15-18 (MRSA)	CPT	fC_{6h} (4)	-1.45	-4.35*	-1.65	-4.07
		fC_{4h} (6)	-1.39	-4.34*	-1.60	-3.98
		fC_{max} (16)	-1.54	-4.43*	-1.89	-4.80
	VAN	fC_{6h} (15)	-1.21	-4.38*	-0.63	-4.41
		fC_{max} (30)	-1.22	-4.34*	-0.85	-5.38
710-5-53 (MRSA)	CPT	fC_{6h} (4)	-0.85	-3.02	-0.80	-2.80
		fC_{4h} (6)	-0.89	-3.55	-1.00	-3.00
		fC_{max} (16)	-1.06	-4.00*	-1.08	-3.10
	VAN	fC_{6h} (15)	-1.57	-4.00*	-1.31	-3.51
		fC_{max} (30)	-1.78	-4.02*	-1.42	-4.29
PEG-10-62-55 (MRSA)	CPT	fC_{6h} (4)	-1.05	-3.02	-1.23	-2.54
		fC_{4h} (6)	-1.07	-3.37	-1.35	-2.60
		fC_{max} (16)	-1.27	-4.03	-1.43	-2.80
	VAN	fC_{6h} (15)	-0.96	-4.26*	-0.61	-2.65
		fC_{max} (30)	-1.05	-4.30*	-0.72	-3.08
MU3 (hVISA)	CPT	fC_{6h} (4)	-2.70	-4.20	-2.94	-4.90
		fC_{4h} (6)	-2.95	-4.49*	-3.14	-5.00
		fC_{max} (16)	-3.60	-4.50*	-3.29	-4.99
	VAN	fC_{6h} (15)	-1.20	-4.20	-1.13	-3.10
		fC_{max} (30)	-1.88	-4.26	-1.16	-3.08
MU50 (VISA)	CPT	fC_{6h} (4)	-3.18	-4.47*	-2.02	-5.10
		fC_{4h} (6)	-3.46	-4.53*	-2.17	-5.61
		fC_{max} (16)	-4.02	-4.46*	-2.24	-5.96
	VAN	fC_{6h} (15)	-0.76	-4.23	-0.59	-2.47
		fC_{max} (30)	-0.87	-4.46*	-0.58	-4.06

Abbreviations: CPT, ceftaroline; VAN, vancomycin; conc., concentration

*below limit of detection (<20 CFU/mL); numbers in bold indicate a bactericidal effect

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