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Objectives: Ceftaroline (CPT) fosamil, a water-soluble prodrug of CPT, has been approved by the European Medicines Agency for treatment of adults with complicated skin and soft tissue infections (cSSSI) and community-acquired pneumonia. CPT has been shown to have a broad-spectrum of antimicrobial activity including methicillin-resistant *Staphylococcus aureus* (MRSA). CPT 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 MRSA by time-kill methodology. Concentrations (conc.) used were those corresponding to human peak free serum conc. (fC_{max}) as well as conc. corresponding to the free-drug conc. achieved for 40–50% of the dosing interval.

Methods: MICs were determined by the broth microdilution (BMD) procedure according to the standard ISO 20776-1. Time-kill assays were performed in glass flasks containing 20 mL of cation-adjusted Mueller-Hinton-broth at starting inocula of appr. 5×10^5 colony-forming units (CFU)/mL (low inoculum) or 5×10^7 CFU/mL (high inoculum). Final conc. were 16 / 6 / 4 mg/l for CPT, 12 / 1.5 mg/L for FLU and 30 / 15 mg/L for VAN being consistent with 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. CPT was tested against all strains (2 MSSA, 6 MRSA), while FLU and VAN were tested against MSSA and MRSA, respectively. All experiments were performed in duplicate. Details on the test organisms are given in the Table.

Results: With both inocula, CPT caused comparable killing activity to FLU (MSSA) and VAN (MRSA), but CPT usually displayed a more rapid killing effect within the first 6 h, as compared to VAN. This effect was most pronounced for strains Mu3 (hVISA) and Mu50 (VISA). In contrast, MRSA strain 710-5-53 (CPT MIC 2 mg/L) was less rapidly killed during the first hours after exposure. Diminished activity of test organisms to either CPT or VAN, however, did not largely reduce the extent of killing. Even a conc. comparable to the MIC, as seen for VAN against Mu50, provided a kill of $>2 \log_{10}$ CFU/ml by 24 h. Changes in viable counts determined at 24 h after exposure to the study drugs are displayed in the Table.

Conclusions: CPT at clinically achievable levels showed 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 VAN.

Table: Changes in viable counts (log₁₀ CFU/mL) at 24 h

Organism (Characteristics)	MIC (mg/l) CPT / FLU or VAN	CPT		FLU		VAN	
		fC_{max} / fC_{4h} / fC_{6h} 16 mg/l / 6 mg/l / 4 mg/l	fC_{max} / fC_{4h} 12 mg / 1.5 mg/l	fC_{max} / fC_{4h} 30 mg/l / 15 mg/l	fC_{max} / fC_{6h} 30 mg/l / 15 mg/l		
ATCC 29213 (MSSA)	L: 0.25 / <u>0.25</u> H: 0.5-1 / <u>0.25-0.5</u>	L: -4.1 / -3.3 / -3.5 H: -2.6 / -2.4 / -2.3	L: -3.2 / -2.6 H: -2.8 / -2.5	-	-		
CR-2-33 (MSSA, blood culture isolate)	L: 0.25 / <u>0.25</u> H: 0.25 / <u>0.5</u>	L: -4.2 / -4.3 / -4.2 H: -6.1* / -6.1* / -6.1*	L: -4.2 / -3.5 H: -6.1* / -4.6	-	-		
CR-5-81 (MRSA, blood culture isolate, spa t003)	L: 0.5 / 1 H: 1 / 2	L: -4.2* / -4.2* / -4.2* H: -3.3 / -2.8 / -2.8	-	L: -4.2* / -4.2* H: -3.0 / -2.9	-		
CR-15-18 (MRSA, blood culture isolate, spa t032)	L: 1 / 1 H: 1 / 2	L: -4.4 / -4.3 / -4.4 H: -4.8 / -4.0 / -4.0	-	L: -4.3* / -4.4* H: -5.4 / -4.4	-		
710-5-53 (MRSA, blood culture isolate, spa t1068)	L: 2 / 0.5 H: 2 / 2	L: -4.0* / -3.6 / -3.0 H: -3.1 / -3.0 / -2.8	-	L: -4.0* / -4.0* H: -4.3 / -3.5	-		
PEG-10-62-55 (MRSA, USA300, t008)	L: 0.5-1 / 0.5 H: 1-2 / 2	L: -4.0 / -3.4 / -3.0 H: -2.8 / -2.6 / -2.5	-	L: -4.3* / -4.3* H: -3.1* / -2.7	-		
MU50 (MRSA, VISA)	L: 1 / 4-8 H: 2 / 8-16	L: -4.5* / -4.5* / -4.5* H: -6.0 / -5.6 / -5.1	-	L: -4.5* / -4.2 H: -4.1 / -2.5	-		
MU3 (MRSA, hVISA)	L: 1 / 2-4 H: 2 / 4	L: -4.5* / -4.5* / -4.2 H: -5.0 / -5.0 / -4.9	-	L: -4.3 / -4.2 H: -3.1 / -3.1	-		

Abbreviations: L, low inoculum; H, high inoculum; *below limit of detection