A-628

Assessment of the Antistaphylococcal Effect of Ceftaroline in Long Duration Human Dose Simulations: Impact of MIC

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Abstract

Background: Ceftaroline (CPT) is effective and well tolerated in randomised controlled trials of patients with skin and skin structure infections – many of whom are infected with *Staphylococcus aureus* [MSSA or MRSA]. For *S. aureus* from clinical trials, CPT MICs are in the range 0.06–2 mg/L. However, the number of strains with MIC >1 mg/L are small. *S. aureus* strains with MICs of up to 2 mg/L respond well to humanised dosing of CPT in pre clinical models over 24–48 h – the impact of longer drug exposures such as occur in man is unclear. We used an *in vitro* pharmacokinetic model (IVPM) to simulate free drug serum concentrations associated with 600 mg BD dosing for 4 days (96h) and studied the antibacterial effect (ABE) against *S. aureus* with MICs in the range 0.12–2.0 mg/L.

Methods: A dilution single compartment IVPM was used. 8 strains of *S. aureus* (3 MSSA, 5 MRSA) CPT MICs of 0.12 to 2 mg/L were used. The pharmacokinetic profile was based on human dosing of 600 mg Q12h (free drug C_{max} 19.0 mg/L (1 h), $T_{½}$ 2.5 h). ABE was measured by change in viable count at 24 h (d24), 48 h (d48), 72 h (d72), 96 h (d96) relative to the starting inocula (log CFU/mL). Area under the bacterial kill curve (AUBKC) was calculated at 24, 48, 72 and 96 h (log CFU/mL.h). Risk of resistance was assessed by population profiles on x1, x2 and x4 CPT MIC nutrient agar plates.

Results: The ABE is shown below.

CPT MIC (mg/L)	T>MIC(%)	Phenotype	d48 (log CFU/mL)	AUBKC48 (log CFU/mL.h)	d96 (log CFU/mL)	AUBKC96 (log CFU/mL.h)
0.12	100	MSSA	-3.3 ± 1.0	29 ± 4	-1.9 ± 2.1	116 ± 72
0.12	100	MSSA	-3.3 ± 1.2	33 ± 6	-0.7 ± 1.1	125 ± 83
0.25	100	MRSA	-3.5 ± 0.4	29 ± 9	-4.1 ± 0.3	44 ± 18
0.25	100	MRSA	-3.8 ± 0.5	25 ± 3	-4.3 ± 0.1	40 ± 2
1.0	100	MSSA	-4.0 ± 0.5	22 ± 5	-3.9 ± 0.7	34 ± 6
1.0	100	MRSA	-3.8 ± 0.5	20 ± 1	-3.7 ± 0.6	35 ± 6
1.5	95	MRSA	-3.9 ± 0.4	36 ± 10	-2.6 ± 1.5	76 ± 45
2.0	82	MRSA	-3.5 ± 1.0	40 ± 8	-2.0	89 ± 22

There was no significant difference between the ABE of CPT based on MIC (ANOVA p>0.05). There was no emergence of resistance, including those strains where some regrowth occurred at 96 h.

Conclusions: These data show that in a pre-clinical model, CPT 600 mg BD simulations over 96 h are equally effective against *S. aureus* with MICs up to 2 mg/L.

Introduction

- Ceftaroline fosamil, the pro-drug of ceftaroline, has been approved by the FDA for the treatment of acute bacterial skin and skin-structure infections (ABSSSI) and community-acquired bacterial pneumonia.
- The 24-h ƒT>MIC (the time the free drug plasma concentration of the drug is above the MIC) is the dominant pharmacodynamic driver in pre-clinical infection models for cephalosporins.
- Pharmacodynamic analysis of ceftaroline fosamil for ABSSSI has indicated high target attainment rates for *Staphylococcus aureus* strains up to 2 mg/L. However, *S. aureus* ƒT>MIC targets were based on only four *S. aureus* strains and the antibacterial effect of prolonged ceftaroline dosing plus the risks of emergence of resistance were not assessed.
- The aim of this study was to describe the antibacterial effect of ceftaroline against *S. aureus* strains with a range of ceftaroline MICs in long term human dose simulation experiments. In addition, the relationship between ƒT>MIC and antibacterial effect and risk of changes in population profiles was established for both methicillin-sensitive *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA).

Methods

- A dilutional *in vitro* pharmacokinetic model was used to simulate average free drug serum concentrations of ceftaroline associated with 600 mg q12h ceftaroline fosamil dosing in humans (C_{max} 19.0 mg/L, T_{max} 1 h, $T_{½}$ 2.5 h).
- All pharmacokinetic simulations of human doses to determine antibacterial effect and changes in population analysis profiles were performed at least in triplicate.
- Eight strains of *S. aureus* were used: three MSSA (ceftaroline MIC 0.12–1.0 mg/L) and five MRSA (ceftaroline MIC 0.25–2.0 mg/L).
- Antibacterial effect was measured by log change in viable count at 24 h (d24), 48 h (d48), 72 h (d72) and 96 h (d96) relative to the starting inocula (log CFU/mL). Area under the bacterial kill curve (AUBKC) was calculated at 24, 48, 72 and 96 h (log CFU/mL.h).
- Emergence of resistance for each strain was assessed by changes in population analysis profiles on nutrient agar plates containing x1, x2 and x4 the ceftaroline MIC at 24, 48, 72 and 96 h. The limit of detection was 10^2 CFU/mL.

Results

- The antibacterial effect is shown in the Table and Figures 1a – h.
- Ceftaroline produced a >3 $\log_{10}$ drop in staphylococcal viable count at 48 h in all strains. MIC was not related to log drop in viable count.
- At 96 h four strains (two MSSA and two MRSA) showed some regrowth. Four strains had a >3.5 log reduction in viable count.
- Log change in viable count and AUBKC was not related to ceftaroline MIC. No significant difference was observed between the antibacterial effect of ceftaroline based on MIC (ANOVA p>0.05).
- No emergence of resistance occurred, including those simulations where some regrowth occurred at 96 h.

Figures 1a – d. The antibacterial effect of ceftaroline against MSSA and MRSA strains (MICs 0.12–0.25 mg/L) over 96 h

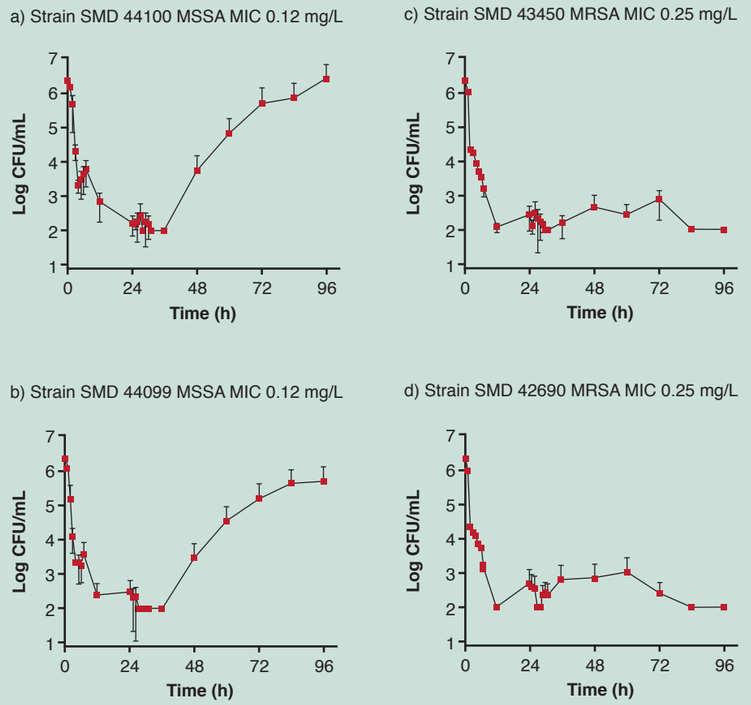
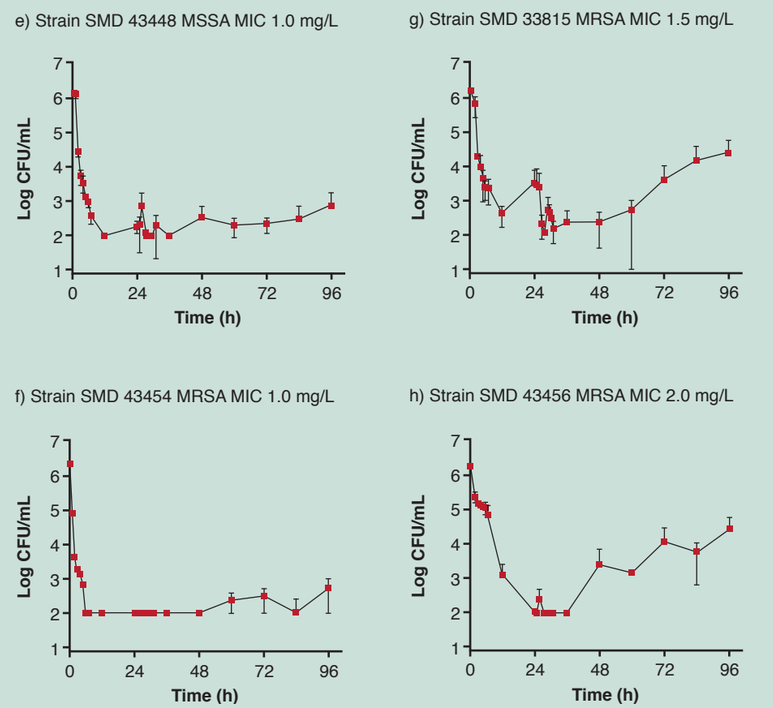


Table. The antibacterial effect and T>MIC of ceftaroline against MSSA and MRSA strains at 48 h and 96 h

Strain	Ceftaroline MIC (mg/L)	T>MIC(%)	Phenotype	d48 (log CFU/mL)	AUBKC48 (log CFU/mL.h)	d96 (log CFU/mL)	AUBKC96 (log CFU/mL.h)
44100	0.12	100	MSSA	-3.3 ± 1.0	29 ± 4	-1.9 ± 2.1	116 ± 72
44099	0.12	100	MSSA	-3.3 ± 1.2	33 ± 6	-0.7 ± 1.1	125 ± 83
43450	0.25	100	MRSA	-3.5 ± 0.4	29 ± 9	-4.1 ± 0.3	44 ± 18
42690	0.25	100	MRSA	-3.8 ± 0.5	25 ± 3	-4.3 ± 0.1	40 ± 2
43448	1.0	100	MSSA	-4.0 ± 0.5	22 ± 5	-3.9 ± 0.7	34 ± 6
43454	1.0	100	MRSA	-3.8 ± 0.5	20 ± 1	-3.7 ± 0.6	35 ± 6
33815	1.5	95	MRSA	-3.9 ± 0.4	36 ± 10	-2.6 ± 1.5	76 ± 45
43456	2.0	82	MRSA	-3.5 ± 1.0	40 ± 8	-2.0	89 ± 22

Figures 1e – h. The antibacterial effect of ceftaroline against MSSA and MRSA strains (MICs 1.0–2.0 mg/L) over 96 h



Conclusion

- In conclusion, these data from an *in vitro* pharmacokinetic model validate the use of ceftaroline fosamil 600 mg q12h IV to treat *S. aureus* strains with MIC ≤2 mg/L.

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