Pharmacodynamics of Ceftaroline against Staphylococcus aureus: Studied in an In Vitro Pharmacokinetic Infection Model

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Updated abstract

Background: Ceftaroline (CPT) is an extended-spectrum cephalosporin which has been recently approved in the US for clinical use in acute bacterial skin and skin-structure infections. CPT has in vitro and in vivo clinical activity against MRSA. The CPT MICs for Staphylococcus aureus (SA) were established for antibacterial effect using a small number of strains in acute animal infection models. In 24 h drug exposures. Our aim was to establish the CPT MIC exposure targets for antibacterial effect up to 96 h – more closely mimicking human exposures – and evaluate the risk of changes in population analysis profiles (PAPs) with changes in CPT exposure and time.

Methods: A dilutional in vitro PK model was used to simulate CPT/TF (MIC) in the range 0–100%, using 9–11 exposures per SA strain over 96 h. Pharmacokinetic profiles were based on a human dosing of 800 mg by IM CPT, 190 mg/L T1/2, 2.5 h. Four strains of MSSA (CPT MICs 0.12–1.0 mg/L) and 4 MRSA strains (CPT MICs 0.25–2.0 mg/L) were used. Population analysis profiles (PAPs) were assessed 24 h by inoculation onto agar plates containing CPT, x4 and x MIC. CPT, TF, MRSA interactions and clinical effects were determined for each strain by fitting a sigmoid Emax curve. Results: The CPT-MIC (mean = SD) for a 24 h static effect and -1 log drop for MSSA were 27 ± 1% and 31 ± 12% respectively. Equivalent values for MRSA were 22 ± 9% and 25 ± 7%. For all SA strains, a CPT-MIC of 32 ± 8% was associated with a -3 log kill at 24 h. Static effect exposures increased stability over time to 33 ± 8% at 48 h, 35 ± 9% at 72 h and 43 ± 13% at 96 h. A CPT-MIC of 54 ± 20% produced a -3 log kill at 96 h. Changes in PAP indicated by growth on MICx4 plates were absent at 48 h. At 96 h, growth on MICx4 plates occurred in the majority of experiments with CPT-MIC > x4 MIC. The highest counts occurred in the range 20–40%.

Conclusions: CPT exposure targets for CPT and MRSA are the same. A CPT-MIC of 15–25% at 24 h and 20–40% with a -1 log kill: A CPT-MIC of 50% suppressed changes in PAP over 96 h.

Introduction

- Ceftaroline, the active form of ceftaroline fonsas, is an N-phosphonomethyl cephalosporin with broad-spectrum in vitro and in vivo activity against Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA).
- MIC (MICxMICxMIC) to MRSA are 0.5–10, 2, and 4 mg/L, respectively. Equil. values for MSSA were 22 ± 9% and 25 ± 7%.
- The 600 mg q12h doses of ceftaroline fonsas used in clinical trials produced peak concentrations of about 20 mg/L after a 1 h infusion, T1/2, 2.5 h, and AUC0-24h, 190 mg/L.
- The 24 h CPT-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.
- Ceftaroline fonsas has been shown to be non-inferior to vancomycin plus aminoglycosin in the therapy of complicated skin and skin-structure infections in randomized clinical trials.
- Many patients recruited into these clinical trials had infections due to MRSA or MSSA.

Methods

- A dilutional in vitro pharmacokinetic model was used to simulate average free drug serum concentrations of ceftaroline fonsas with 600 mg q12h in man. Dose-ranging ensured a CPT-MIC of 0–100% in exposure response experiments.
- Eight strains of S. aureus were used: four MSSA (ceftaroline MIC 0.12–1.0 mg/L) and four MRSA (ceftaroline MIC 0.25–2.0 mg/L). Antibacterial effect was measured by log change in viable count. Emergence of resistance for each strain was assessed by changes in population analysis profiles (PAPs). In nutrient agar plates containing x1, x4, and x MIC, CPT, MRSA, and MSSA interactions and clinical effects were determined for each strain by fitting a sigmoid Emax curve. Results: The CPT-MIC (mean = SD) for a 24 h static effect and -1 log drop for MSSA were 27 ± 1% and 31 ± 12% respectively. Equivalent values for MRSA were 22 ± 9% and 25 ± 7%. For all SA strains, a CPT-MIC of 32 ± 8% was associated with a -3 log kill at 24 h. Static effect exposures increased stability over time to 33 ± 8% at 48 h, 35 ± 9% at 72 h and 43 ± 13% at 96 h. A CPT-MIC of 54 ± 20% produced a -3 log kill at 96 h. Changes in PAP indicated by growth on MICx4 plates were absent at 48 h. At 96 h, growth on MICx4 plates occurred in the majority of experiments with CPT-MIC > x4 MIC. The highest counts occurred in the range 20–40%.

Conclusions: CPT exposure targets for CPT and MRSA are the same. A CPT-MIC of 15–25% at 24 h and 20–40% with a -1 log kill: A CPT-MIC of 50% suppressed changes in PAP over 96 h.

Results

- The CPT-MIC (MIC) relationship to antibacterial effect at 24 h is shown in Table 1 and Figure 1.
- The mean CPT-MIC relationship to antibacterial effect at 24 h, 48 h and 96 h is shown in Table 2 and 3. A CPT-MIC of 24.5 ± 8.9% is associated with a -4 log bacterial effect and a CPT-MIC of 27.8 ± 9.5% with a -1 log drop for S. aureus. There was no difference between MRSA and MSSA strains (p<0.05).
- The CPT-MIC for killing are greater at 48 h and 96 h compared with 24 h.

Table 1. CPT-MIC to antibacterial effect for ceftaroline at 24 h

<table>
<thead>
<tr>
<th>Strain</th>
<th>MSSA</th>
<th>MRSA</th>
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<tr>
<td>CPT MIC</td>
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<td>0.5</td>
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<td>4.0</td>
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- CPT-MIC exposures of ≤40%. The relationship between CPT-MIC and changes in PAPs are shown in Table 4.

Table 4. Changes in ceftaroline population profiles in S. aureus at 48 h and 96 h drug exposure

<table>
<thead>
<tr>
<th>Strain</th>
<th>MSSA</th>
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<tr>
<td>CPT MIC</td>
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<td>0.12</td>
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- The risk of emergence of resistance, as indicated by changes in PAPs, showed that a CPT-MIC of 30% for 48 h or 50% for 96 h is necessary to suppress changes for S. aureus.

Conclusions

- These CPT-MIC data are in agreement with previous animal data.1,2,3
- A CPT-MIC target of 25–30% would seem reasonable for clinical breakpoint settings for ceftaroline against S. aureus. A CPT-MIC of 50% would moderate the risk of emergence of resistance as noted in changes in MIC population analysis profiles.

References


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