A2-555

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

Alan R Noel, Karen E Bowker, Sharon G Tomaselli, Alasdair P MacGowan

Bristol Centre for Antimicrobial Research & Evaluation (BCARE), North Bristol NHS Trust & University of Bristol, Bristol, UK

Contact Information:
Alasdair P MacGowan
BCARE
Department of Medical Microbiology
Lime Walk Building
Southmead Hospital
Westbury-on-Trym
Bristol, BS10 5NB, UK
Tel: +44 (0) 117 323 5651/2
Fax: +44 (0) 117 323 8332
Email: alasdair.macgowan@nbt.nhs.uk

Updated abstract

Background: Ceftaroline (CPT) is an extended-spectrum IV cephalosporin which has been recently approved in the US for clinical use in acute bacterial skin and skin-structure infections. CPT has *in vitro*, *in vivo* and clinical activity against MRSA. The ƒT>MIC targets for *Staphylococcus aureus* (SA) were established for antibacterial effect using a small number of strains in acute animal infection models over 24 h drug exposures. Our aim was to determine ƒT>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 (PAP) with changes in CPT exposure and time.

Methods: A dilutional *in vitro* PK model was used to simulate CPT ƒT>MIC in the range 0–100%, using 9–11 exposures per SA strain over 96 h. Pharmacokinetic profiles were based on human dosing of 600 mg 12 hly (C_{max} 19.0 mg/L, $T_{½}$ 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 hly by inoculation onto agar plates containing CPT 2x, 4x and 8x MIC. ƒT>MIC exposures for bacteriostatic and cidal effects were determined for each strain by fitting a sigmoid E_{max} curve.

Results: The ƒT>MIC (mean ± SD) for a 24 h static effect and -1 log drop for MSSA were 27 ± 10% and 31 ± 12% respectively. Equivalent values for MRSA were 22 ± 9% and 25 ± 7%. For all SA strains, a ƒT>MIC of 32 ± 8% was associated with a -3 log kill at 24 h. Static effect exposures increased modestly over time to 33 ± 8% at 48 h, 35 ± 9% at 72 h and 43 ± 13% at 96 h. A ƒT>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 ƒT>MIC exposures of ≤40%. The highest counts occurred in the range 20–40%.

Conclusions: ƒT>MIC exposure targets for CPT with MRSA and MSSA are the same. A ƒT>MIC of 15–30% at 24 h is associated with a bacteriostatic effect and 20–40% with -1 log kill. A ƒT>MIC of ≥50% suppressed changes in PAP over 96 h.

Introduction

- Ceftaroline, the active form of ceftaroline fosamil, is an N-phosphono cephalosporin with broad-spectrum *in vitro*, *in vivo* and clinical activity against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).
- MICs (MIC_{50}/MIC_{90}) to MRSA are 0.5–1.0/1–2 mg/L and methicillin-susceptible *S. aureus* (MSSA) 0.25/0.5 mg/L.[1,2]
- The 600 mg q12h doses of ceftaroline fosamil used in clinical trials produced peak concentrations of about 20 mg/L after a 1 h infusion, $t_{½}$ of 2.5 h and $AUC_{0\text{-}12h}$ of 56 mg/L·h.
- 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.[3]
- Ceftaroline fosamil has been shown to be non-inferior to vancomycin plus aztreonam in the therapy of complicated skin and skin-structure infection in randomized controlled trials.[4]
- Many patients recruited into these clinical trials had infections due to MSSA or MRSA.

Methods

- A dilutional *in vitro* pharmacokinetic model was used to simulate average free drug serum concentrations of ceftaroline associated with 600 mg q12h in man. Dose ranging ensured a ƒT>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 (PAP) on nutrient agar plates containing x1, x2 and x4 the ceftaroline MIC.

Results

- The mean ƒT>MIC relationship to antibacterial effect at 24 h is shown in Table 1 and Figure 1.
- The mean ƒT>MIC relationship to antibacterial effect at 24 h, 48 h and 96 h are shown in Tables 2 and 3.
- A ƒT>MIC of 24.5 ± 8.9% is associated with a 24 h bacteriostatic effect and a ƒT>MIC of 27.8 ± 9.5% with a -1 log drop for *S. aureus*. There was no difference between MSSA and MRSA strains (p<0.05).
- ƒT>MIC targets for killing are greater at 48 h and 96 h compared with 24 h.
- The relationships between ƒT>MIC and changes in PAPs are shown in Table 4.
- The risk of emergence of resistance, as indicated by changes in PAPs, show that a ƒT>MIC of ≥30% for 48 h or >50% for 96 h are necessary to suppress changes for *S. aureus*.

Figure 1. ƒT>MIC relationship of ceftaroline to change in viable counts of *S. aureus* at 24 h exposure

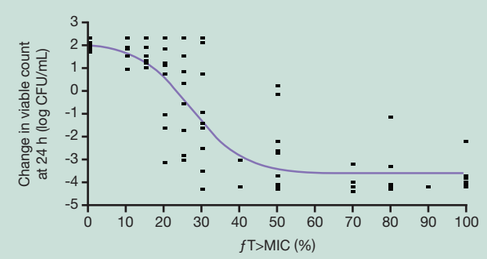

Table 1. ƒT>MIC relationship to antibacterial effect for ceftaroline at 24 h

	MSSA					MRSA					
Antibacterial effect at 24 h	**Strain 44100 MIC 0.12**	**Strain 44099 MIC 0.12**	**Strain 43450 MIC 0.25**	**Strain 43448 MIC 1.0**	**All MSSA**	**Strain 42690 MIC 0.25**	**Strain 43454 MIC 1.0**	**Strain 33815 MIC 1.5**	**Strain 43456 MIC 2.0**	**All MRSA**	**All *S. aureus***
Static	40.0	26.2	24.0	17.0	26.8 ± 9.6	29.0	31.0	12.8	17.0	22.4 ± 8.9	24.5 ± 8.9
-1 log drop	47.1	28.5	29.0	19.0	30.9 ± 11.7	29.0	32.0	20.1	18.0	24.8 ± 6.8	27.8 ± 9.5
-2 log drop	–	31.5	32.0	21.0	28.2 ± 6.2 (n=3)	30.0	33.0	28.2	18.5	27.4 ± 6.2	27.7 ± 5.7 (n=7)
-3 log drop	–	36.9	39.0	23.0	32.9 ± 8.9 (n=3)	30.0	34.0	41.6	20.0	31.4 ± 9.0 (n=3)	32.1 ± 8.1 (n=7)
-4 log drop	–	–	51.0	29.0	–	31.0	38.0	69.1	–	46.0 ± 20.3 (n=3)	37.6 ± 18.6 (n=5)

Table 2. ƒT>MIC relationship to antibacterial effect for ceftaroline at 48 h

	MSSA					MRSA					
Antibacterial effect at 48 h	**Strain 44100 MIC 0.12**	**Strain 44099 MIC 0.12**	**Strain 43450 MIC 0.25**	**Strain 43448 MIC 1.0**	**All MSSA**	**Strain 42690 MIC 0.25**	**Strain 43454 MIC 1.0**	**Strain 33815 MIC 1.5**	**Strain 43456 MIC 2.0**	**All MRSA**	**All *S. aureus***
Static	44.3	36.2	34.0	28.0	35.6 ± 6.7	38.0	31.0	34.9	19.0	30.7 ± 8.3	33.2 ± 7.5
-1 log drop	52.3	41.6	36.0	29.0	39.7 ± 9.8	39.0	31.0	44.3	19.5	33.4 ± 10.8	36.6 ± 10.1
-2 log drop	67.1	48.3	38.0	30.0	45.9 ± 16.0	40.0	31.0	53.0	20.0	36.0 ± 14.0	40.9 ± 14.9
-3 log drop	–	59.1	42.0	31.0	44.0 ± 14.2 (n=3)	42.0	31.0	63.1	20.5	39.1 ± 18.2	41.2 ± 14.9 (n=7)
-4 log drop	–	–	–	–	–	–	32.0	79.2	–	–	–

Table 3. ƒT>MIC relationship to antibacterial effect for ceftaroline at 96 h

	MSSA					MRSA					
Antibacterial effect at 96 h	**Strain 44100 MIC 0.12**	**Strain 44099 MIC 0.12**	**Strain 43450 MIC 0.25**	**Strain 43448 MIC 1.0**	**All MSSA**	**Strain 42690 MIC 0.25**	**Strain 43454 MIC 1.0**	**Strain 33815 MIC 1.5**	**Strain 43456 MIC 2.0**	**All MRSA**	**All *S. aureus***
Static	71.1	38.9	43.0	38.0	47.8 ± 15.8	38.0	36.0	52.3	26.2	38.1 ± 10.8	42.9 ± 13.5
-1 log drop	76.6	48.3	45.0	39.0	52.2 ± 16.7	39.0	37.0	56.4	27.5	40.0 ± 12.0	46.1 ± 15.0
-2 log drop	81.2	58.4	48.0	41.0	57.2 ± 17.6	40.0	38.0	59.7	28.5	41.6 ± 13.1	49.3 ± 16.6
-3 log drop	91.3	71.1	51.0	42.0	63.8 ± 22.0	41.0	39.0	64.4	30.2	43.7 ± 14.6	53.7 ± 20.4
-4 log drop	–	–	62.0	46.0	–	–	–	86.6	34.9	–	57.3 ± 22.4 (n=4)

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

ƒT>MIC	**Number of experiments**	**Number with growth on MICx2 plates**	**Count on MICx2 plates (log CFU/mL)**	**Number with growth on MICx4 plates**	**Count on MICx4 plates (log CFU/mL)**
At 48 h					
≥90	15	0	<2	0	<2
≥70	6	0	<2	0	<2
≥50	8	0	<2	0	<2
≥40	5	1	2.7	1	2.1
≥30	8	2	3.9	0	<2
≥25	8	4	4.4 ± 2.0	0	<2
≥20	8	5	4.3 ± 1.8	0	<2
≥15	7	4	5.2 ± 2.1	0	<2
≥10	7	2	4.7	0	<2
At 96 h					
≥90	15	0	<2	0	<2
≥70	6	1	2.5	0	<2
≥50	8	1	2.5	0	<2
≥40	5	3	3.4 ± 1.6	1	2.1
≥30	8	5	7.1 ± 1.0	4	4.8 ± 2.3
≥25	8	6	5.5 ± 1.4	4	4.6 ± 2.3
≥20	8	6	6.1 ± 1.7	4	4.3 ± 1.6
≥15	7	5	5.6 ± 2.6	3	3.9 ± 1.7
≥10	7	5	6.4 ± 2.3	4	3.7 ± 1.4

Conclusions

- These ƒT>MIC data are in agreement with previous animal data.[1,5]
- A ƒT>MIC target of 25–30% would seem reasonable for clinical breakpoint setting for ceftaroline and *S. aureus*. A ƒT>MIC of ≥50% would minimize the risk of emergence of resistance as noted in changes in MIC population analysis profiles.

References

1. Sader HS et al. *Antimicrob Agents Chemother*. 2005;49:3501–3512.
2. Sader HS et al. *Antimicrob Agents Chemother*. 2008;52:1153–1155.
3. Andes D, Craig WA. *Antimicrob Agents Chemother*. 2006;50:1376–1383.
4. Corey GR et al. *Clin Infect Dis*. 2010;51:641–650.
5. Keel RA et al. *Antimicrob Agents Chemother*. 2011;55:4028–4032.

Acknowledgements

This work was supported by AstraZeneca. We would like to thank JMI laboratories for supplying two MRSA and two MSSA strains.

Presented at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17–20, 2011, Chicago, IL, USA
Poster typesetting and printing was provided by Prime Medica Ltd, Knutsford, Cheshire, UK, and funded by AstraZeneca

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

Alan R Noel, Karen E Bowker, Sharon G Tomaselli, Alasdair P MacGowan

Bristol Centre for Antimicrobial Research & Evaluation (BCARE), North Bristol NHS Trust & University of Bristol, Bristol, UK

Presented at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17–20, 2011, Chicago, IL, USA.