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Pharmacodynamics of Ceftaroline Against *Proteus mirabilis* Pre-clinical Clinical Correlates

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Abstract

Background: Previously, we showed using an in vitro pharmacokinetic (PK) model of infection, that the %*f*T>MIC for ceftaroline (CPT), the active metabolite of ceftaroline fosamil (CPT-F), against *Proteus mirabilis* (Pm) was highly variable between strains. The %T>MIC for a 2 log drop in viable count at 24 h for four Pm strains (CPT MIC ≤0.5mg/L) varied for 14.1% to 74.1% mean±SD 41.3%±25.5 (%CV 62%). Combined data from the CANVAS 1 and 2 studies (NCT00424190 and NCT00423657) of CPT-F versus vancomycin plus aztreonam in patients with complicated skin and skin structure infections with Pm isolated as the primary pathogen at baseline indicated cure rates of 10/15 (67%) patients in the CPT-F arm and 20/21 (95%) in the comparator. Given the variability of T>MIC targets we tested three available strains of Pm from clinical failures to assess their exposure response relationships in our in vitro PK model.

Methods: An in vitro dilutional single compartment model was used to perform dose ranging experiments with CPT ($t_{½}$ 2 h) against three strains of Pm from patients classified as clinical failures; CPT MICs were 0.06, 0.06, and 0.12 mg/L. %*f*T>MIC for 24 h static, -1 log, and -2 log reduction in bacterial load were calculated.

Results: The %*f*T>MIC for the three Pm strains at 24 h were 55.2±10.2 (%CV 18.5) for static effect; 57.8±11.3 (%CV 19.6) for -1 log drop; and 60.5±13.0 (%CV 21.5) for -2 log drop. With one strain (CPT MIC 0.06mg/L) a stable mutant (CPT MIC 0.5 mg/L) emerged after 24 h during dose ranging experiments. This strain was ESBL, AmpC and MBL negative on testing. When this strain was tested in dose ranging experiments the %*f*T>MICs for 24 h static, -1 log, and -2 log drop were 34.3%, 35.0%, and 35.6% respectively.

Conclusions: Pm strains from patients who failed CPT-F therapy in the CANVAS 1 and 2 studies had %*f*T>MIC values for a 2 log reduction in viable counts towards the upper limit of values for this species and for one strain a stable mutant with a raised CPT MIC emerged. These data may help explain the clinical response to CPT-F of Pm infections in the CANVAS studies.

Introduction

- Previously, we showed using an in vitro pharmacokinetic model of infection (IVPKM), that the %*f*T>MIC for ceftaroline (CPT), the active metabolite of ceftaroline fosamil (CPT-F), against *Proteus mirabilis* was highly variable between strains.[1]
- The %*f*T>MIC for a 2 log drop in viable count at 24 h for four *P. mirabilis* strains (CPT MIC ≤0.5 mg/L) varied from 14.1% to 74.1%, mean±SD 41.3%±25.5 (%CV 62%).[1]
- Combined data from the CANVAS 1 and 2 studies (NCT00424190 and NCT00423657) of CPT-F versus vancomycin plus aztreonam in patients with complicated skin and skin structure infections with *P. mirabilis* isolated as the primary pathogen at baseline indicated cure rates of 10/15 (67%) patients in the CPT-F arm and 20/21 (95%) in the comparator arm.[2]
- Given the variability of *f*T>MIC targets, we tested three available strains of *P. mirabilis* from clinical failures to assess their exposure-response relationships in our in vitro PK model.

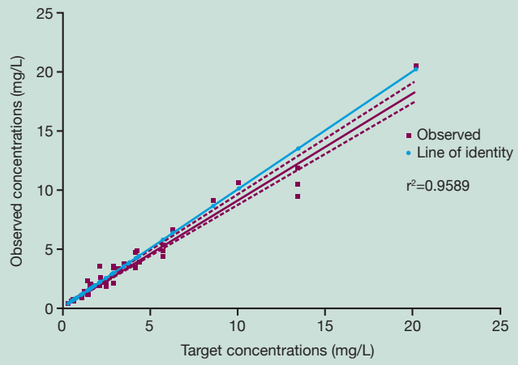
Methods

- A dilutional IVPKM was used to simulate a range of concentrations of CPT to achieve a %*f*T>MIC range of 0–100% for each strain to define the %*f*T>MIC – antibacterial effect relationship. The $t_{½}$ was 2.5 h and dosing was every 12 h (q12h) for 96 h. Between 7–10 doses were simulated per strain. Drug concentrations of CPT were determined by high performance liquid chromatography.
- Three clinical strains of *P. mirabilis* were used: SMH 52235 CPT MIC 0.12 mg/L, SMH 52238 CPT MIC 0.06 mg/L, and SMH 52239 CPT MIC 0.06 mg/L. The inoculum was 10^6 colony forming units (CFU)/mL and experiments were conducted over 96 h.
- 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).
- A sigmoid E_{max} curve was fitted to the data using a Boltzmann Sigmoid E_{max} equation (GraphPad Prism©) to calculate %*f*T>MIC for 24 h static, –1 log, and –2 log reduction in bacterial load.
- Emergence of resistance for each strain was assessed by changes in population analysis profiles on nutrient agar plates containing x2, x4, and x8 the CPT MIC at 0 h, 24 h, 48 h, 72 h, and 96 h. The limit of detection was 10^2 CFU/mL.

Results

- Figure 1 shows the predicted versus observed CPT concentrations.

Figure 1. *Scatter plot of predicted and observed concentrations with 95% confidence interval*



- Figure 2 shows the relationships between CPT %*f*T>MIC and a static, –1 log, –2 log drop in viable count at 24 h for each strain.
- Tables 1–4 show the CPT %*f*T>MIC for a static, –1 log, –2 log drop in viable count at 24 h, 48 h, 72 h, and 96 h for each strain.
- For the three clinical strains the mean %*f*T>MIC for a static effect at 24 h, 48 h, 72 h, and 96 h was 55.2%, 64.7%, 73.9%, and 74.9%, respectively.
- With one strain (SMH 52239 CPT MIC 0.06 mg/L) a stable mutant (SMH 52959 CPT MIC 0.5 mg/L) emerged after 24 h during dose ranging experiments. This strain was extended-spectrum β-lactamase, AmpC, and metallo-β-lactamase negative on testing. When this strain was tested in dose ranging experiments the %*f*T>MICs for 24 h static, –1 log and –2 log drop were 34.3%, 35.0%, and 36.0%, respectively (Figure 1, Tables 1–4).
- Tables 5 and 6 show the growth on x2 MIC, x4 MIC, and x8 MIC recovery plates at 24 h and 96 h. As time increased the amount of growth seen increased; by 96 h in three of four experiments maximal growth was seen on x4 MIC plates between >20% and >50% *f*T>MIC (circa 7.5 log CFU/mL). A similar pattern was observed on x8 MIC plates with growth seen in one of four experiments at a %*f*T>MIC of >90% at 96 h.

Table 1. *%fT>MIC required for a static, –1 log, and –2 log drop at 24 h*

		%*f*T>MIC			
	Strain	MIC (mg/L)	Static effect	-1 log drop	-2 log drop
P. mirabilis	52235	0.12	54.4	60.9	66.5
P. mirabilis	52238	0.06	45.4	45.3	45.6
P. mirabilis	52239	0.06	66.2	67.3	69.4
		Mean	55.2±10.2	57.8±11.3	60.5±13.0
P. mirabilis	52959	0.5	34.3	35.0	35.6

Table 2. *%fT>MIC required for a static, –1 log, and –2 log drop at 48 h*

		%*f*T>MIC			
	Strain	MIC (mg/L)	Static effect	-1 log drop	-2 log drop
P. mirabilis	52235	0.12	74.1	>100	>100
P. mirabilis	52238	0.06	55.3	62.2	75.4
P. mirabilis	52239	0.06	64.8	69.5	>100
		Mean	64.7±9.4	65.9	75.4
P. mirabilis	52959	0.5	52.2	52.7	53.5

Table 3. *%fT>MIC required for a static, –1 log, and –2 log drop at 72 h*

		%*f*T>MIC			
	Strain	MIC (mg/L)	Static effect	-1 log drop	-2 log drop
P. mirabilis	52235	0.12	88.4	>100	>100
P. mirabilis	52238	0.06	65.3	67.3	70.7
P. mirabilis	52239	0.06	67.9	>100	>100
		Mean	73.9±12.7	67.3	70.7
P. mirabilis	52959	0.5	52.1	53.7	54.7

Table 4. *%fT>MIC required for a static, –1 log, and –2 log drop at 96 h*

		%*f*T>MIC			
	Strain	MIC (mg/L)	Static effect	-1 log drop	-2 log drop
P. mirabilis	52235	0.12	98.5	>100	>100
P. mirabilis	52238	0.06	59.4	65.5	71.2
P. mirabilis	52239	0.06	66.8	>100	>100
		Mean	74.9±20.8	65.5	71.2
P. mirabilis	52959	0.5	72.7	73.7	74.9

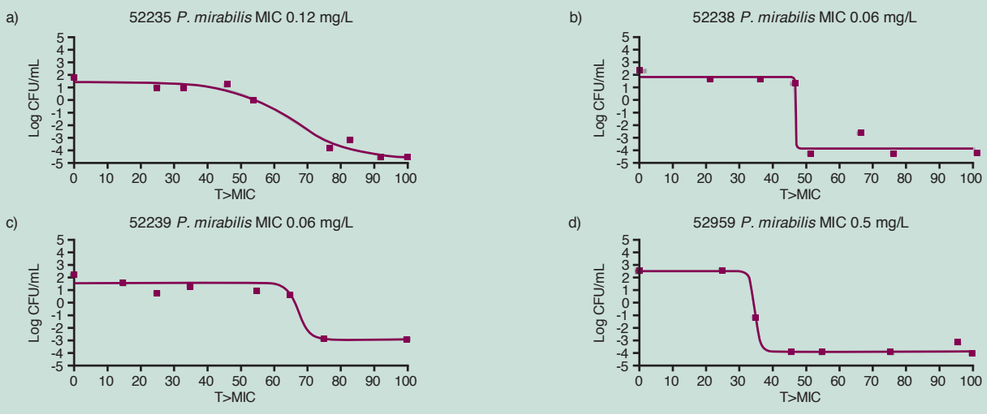
Table 5. *Growth on recovery plates at 24 h*

	MIC x2			MIC x4			MIC x8		
% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)	% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)	% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)
0–20	2/4	3.8	0–20	1/4	3.15	0–20	0/4	–
>20–30	3/4	7.12±0.56	>20–30	0/4	5.25±2.15	>20–30	2/4	6.43
>30–40	3/4	6.30±1.85	>30–40	0/4	6.48	>30–40	2/4	5.33
>40–50	2/4	5.27	>40–50	0/4	6.49	>40–50	1/4	7.4
>50–70	0/4	–	>50–70	0/4	5.6	>50–70	0/4	–
>70–80	0/4	–	>70–80	0/4	–	>70–80	0/4	–
>80–90	0/4	–	>80–90	0/4	–	>80–90	0/4	–
>90–100	0/8	–	>90–100	0/8	–	>90–100	0/8	–

Table 6. *Growth on recovery plates at 96 h*

	MIC x2			MIC x4			MIC x8		
% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)	% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)	% *f*T>MIC	No. of exps >2 log growth	Viable count (log CFU/mL)
0–20	2/4	6.78	0–20	2/4	5.15	0–20	1/4	5.4
>20–30	3/4	8.04±0.31	>20–30	3/4	7.95±0.25	>20–30	3/4	7.28±1.16
>30–40	3/4	7.66±0.58	>30–40	3/4	7.30±0.79	>30–40	3/4	6.70±1.53
>40–50	3/4	7.78±0.29	>40–50	3/4	7.51±0.81	>40–50	3/4	6.34±2.41
>50–70	1/4	8.18	>50–70	2/4	7.69	>50–70	1/4	8.11
>70–80	1/4	7.62	>70–80	2/4	5.37	>70–80	1/4	7.48
>80–90	1/4	8.00	>80–90	1/4	8.04	>80–90	1/4	7.99
>90–100	1/7	7.53	>90–100	1/7	7.56	>90–100	1/7	7.53

Figure 2. *Relationship between antibacterial effect for each strain at 24 h*



Conclusions

- *P. mirabilis* strains from patients who failed CPT-F therapy in the CANVAS 1 and 2 studies had %*f*T>MIC values for a 2 log reduction in viable counts towards the upper limit of values for this species, and for one strain a stable mutant with a raised CPT MIC emerged.
- The data presented here may help explain the clinical response to CPT-F of *P. mirabilis* infections in the CANVAS studies.

Reference

1. Bowker et al. 53rd ICAAC 2013, Denver, Colorado, USA (Poster A464).
2. Corey et al. *Clin Infect Dis* 2010;15;51:641–650.

Disclosures

This study was funded by a grant from AstraZeneca, Waltham, MA, USA.

Poster typesetting was provided by Prime Medica Ltd, Knutsford, Cheshire, UK, funded by AstraZeneca.
Presented at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17–21, 2015, San Diego, CA, USA.

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