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Pharmacodynamics of Ceftaroline against *Enterobacteriaceae*

Karen E Bowker, Alan R Noel, Sharon Tomaselli, Donna L Nicholls, Alasdair P MacGowan

BCARE, North Bristol NHS Trust & University of Bristol, Southmead Hospital, Bristol, UK

Contact Information:
Alan R Noel
Dept of Microbiology
Lime Walk Building
Southmead Hospital
Westbury on Trym
Bristol BS10 5NB
Phone: +44 0117 3234187
Fax: +44 0117 3238332
Alan.Noel@nbt.nhs.uk

Abstract

Background: Ceftaroline (CPT) fosamil, active metabolite CPT, is an anti- MRSA cephalosporin licensed by the US FDA for use in acute skin and skin structure infection and community acquired pneumonia. CPT is also active against non-ESBL producing *Enterobacteriaceae* (Ent) with a similar *in vitro* potency to cefotaxime. The relationship of %T>MIC to antibacterial effect (ABE) assessed by log change in viable count has been described in a number of animal models. esults suggest a wide range of T>MIC targets, but to date it is uncertain what contribution the number and types of strain tested and/or the pharmacodynamic (PD) models make to this variability. We used an in vitro pharmacokinetic model (IVPKM) to study the ABE of CPT on wild type Ent and its impact on population profiles.

Methods: A single compartment dilutional IVPKM was used to simulate a range of *ƒ*T>MIC from 0-100% based on the pharmacokinetics of CPT, 600 mg at q12h. Nine wild type Ent (5 *K. pneumoniae* CPT MIC 0.12–0.75 mg/L and 4 *E. coli* MIC 0.04–0.75mg/L) were used. The inoculum was 10^6 CFU/mL. ABE was assessed by change in viable count (log CFU/mL) and population profiles by culture onto agar plates containing MICx2, x4 and x8 CPT. T>MIC was related to ABE using a Sigmoid E_{max} model.

Results: The mean (SD) *ƒ*T>MIC for static, -1 log, -2 log drop at 24 h are:

24 h effect	%T>MIC		
	E. coli **(n=4)**	***K. pneumoniae*** **(n=5)**	**Combined (n=9)**
Static	35.0 (6.3)	36.1 (8.3)	35.6 (7.0)
-1 log drop	36.8 (7.1)	43.6 (9.1)	40.6 (8.5)
-2 log drop	38.3 (8.3)	52.3 (13.3)	46.1 (13.0)

Results suggest similar 24 h static and cidal effect targets for both species (p>0.1, t test). There was no growth on MIC x4 plates at 0 h for either species. Combining the data for *E. coli* and *K. pneumoniae*, a 24 h T>MIC in the range 0–20% resulted in growth on MIC x4 plates with all experiments; at T>MIC in the range >20–40% in <75% experiments and T>MIC of >40–60% in ≤15% experiments.

Conclusion: The 24 h static to -1 log drop T>MIC target for CPT is 30–40% for both E. coli and K. pneumoniae. This value is similar to other cephalosporins studied in *in vitro* and *in vivo* models. The T>MIC to prevent changes in population profiles is >60%.

Introduction

- Ceftaroline fosamil, the pro-drug of the active metabolite ceftaroline, is an anti-MRSA cephalosporin that has been approved by the FDA for the treatment of acute bacterial skin and skin-structure infections (ABSSSI), including MRSA, and community-acquired bacterial pneumonia (CABP), methicillin-susceptible *S. aureus* but not MRSA.
- Ceftaroline is also active against non-ESBL producing *Enterobacteriaceae* with MIC50s 0.06–0.12mg/L for *Escherichia coli* and *Klebsiella pneumoniae*.
- The 24-h *ƒ*T>MIC (the time the free drug plasma concentration is above the MIC) is the dominant pharmacodynamic (PD) driver in pre-clinical infection models for ceftaroline.
- Neutropenic murine thigh infection models have indicated a range of 24 h *ƒ*T>MIC between 28 and 49% for a static effect and 66 to 73% for -1 log drop at 24 h for *E. coli* and *K. pneumoniae*. It is uncertain what impact the strain type, number and type of PD model may have upon this variability.

Objectives

- The aim of this study was to establish the relationship between *ƒ*T>MIC and antibacterial effect and the risk of changes in population profiles of ceftaroline against *Enterobacteriaceae* strains with a range of ceftaroline MICs.

Methods

- A dilutional *in vitro* pharmacokinetic model was used to simulate a range of *ƒ*T>MIC serum concentrations (0–100%) of ceftaroline based on the pharmacokinetics of 600 mg q12h ceftaroline fosamil dosing in humans.
- Nine wild type strains of *Enterobacteriaceae* were used: five *K. pneumoniae* (ceftaroline MIC 0.12–0.75 mg/L); four *E. coli* (0.04– 0.75 mg/L). The inoculum was 10^6 CFU/mL.
- 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} model was used to relate T>MIC with antibacterial effect using the Boltzmann equation utilising Graph Pad Prism™.
- Changes in population profiles were assessed by growth on nutrient agar plates containing x2, x4 and x8 the ceftaroline MIC at 24 h, 48 h, 72 h and 96 h. The limit of detection was 10^2 CFU/mL.

Results

- Table 1 shows the ceftaroline MIC and *ƒ*T>MIC for a static, -1 log, and -2 log drop in viable count at 24 h for the individual *K. pneumoniae* strains.
- Table 2 shows the ceftaroline MIC and *ƒ*T>MIC for a static, -1 log, and -2 log drop in viable count at 24 h for the individual *E. coli* strains.
- Table 3 shows the changes in population profiles as shown by growth on x2, x4 and x8 ceftaroline MIC plates for all strains at 24 h.

Table 1: Individual *ƒ*T>MIC (%) for *K. pneumoniae* strains at 24 h

strain	MIC (mg/L)	*ƒ*T>MIC (%)		
		static	-1 log drop	-2 log drop
K. pneumoniae 38345	0.75	39.9	46.6	55.3
K. pneumoniae 43739	0.38	26.8	43	63.8
K. pneumoniae 45645	0.25	27.5	28.2	29.5
K. pneumoniae 43489	0.12	42.3	51.0	59.1
K. pneumoniae 45059	0.19	44.0	49.0	53.7
Combined		36.1 ± 8.3	43.6 ± 9.1	52.3 ± 13.3

Table 2: Individual *ƒ*T>MIC (%) for *E. coli* strains at 24 h

strain	MIC (mg/L)	*ƒ*T>MIC (%)		
		static	-1 log drop	-2 log drop
E. coli 44913	0.75	34.9	36.9	38.9
E. coli 44852	0.75	40.6	41.3	41.3
E. coli 44917	0.19	38.3	42.3	46.3
E. coli 44966	0.045	26.2	26.8	26.8
Combined		35.0 ± 6.3	36.8 ± 7.1	38.3 ± 8.3

Table 3. Population profiles on recovery plates at 24 h

*ƒ*T>MIC range	Growth on MICx2 recovery plates		Growth on MICx4 recovery plates		Growth on MICx8 recovery plates	
	No. of exps with >2 log growth (%)	Viable count (log CFU/mL)	No. of exps with >2 log growth (%)	Viable count (log CFU/mL)	No. of exps with >2 log growth (%)	Viable count (log CFU/mL)
0–10	7/14 (50)	5.82 ± 2.80	4/14 (29)	6.48 ± 1.52	2/12	3.52 ± 1.53
>10–20	4/4 (100)	7.14 ± 1.07	4/4 (100)	6.51 ± 1.57	3/4 (75)	4.12 ± 1.23
>20–30	7/8 (88)	6.61 ± 1.70	5/8 (63)	6.66 ± 1.45	4/8 (50)	4.47 ± 0.81
>30–40	8/11 (73)	6.35 ± 1.60	5/11 (45)	5.44 ± 1.29	1/11 (9)	4.37 ± 1.07
>40–50	4/13 (31)	5.82 ± 2.08	2/13 (15)	5.45 ± 0.14	1/13 (8)	3.23
>50–60	2/8 (25)	4.03 ± 1.70	1/8 (13)	5.2	0/8 (0)	
>60–70	0/9 (0)		0/9 (0)		0/9 (0)	
>70–80	0/9 (0)		0/9 (0)		0/9 (0)	
>80–90	0/3 (0		0/3 (0)		0/3 (0)	
>90	0/9 (0)		0/9 (0)		0/9 (0)	

- Figure 1 shows the relationship between *ƒ*T>MIC and *K. pneumoniae*; Figure 2 show the relationship between *ƒ*T>MIC and *E. coli* at 24 h; Figure 3 shows the relationship between *ƒ*T>MIC and all strains tested.
- The *ƒ*T>MIC targets for static and cidal effects for both species were similar (p>0.1, t-test; Tables 1 and 2). The combined target for a static, -1 log and -2 log drop in viable count was 35.6, 40.6 and 46.1, respectively.
- *ƒ*T>MIC was related to the probability and degree of change in population profiles (Table 3).
- Combining the data for all strains, no growth was observed on the x2, x4 or x8 MIC plates at 0 h. At 24 h, a *ƒ*T>MIC of 0–20% resulted in growth on x2 and x4 MIC recovery media in all experiments; 75% of experiments showed growth on x8 MIC plates.

Figure 1. Relationship between *ƒ*T>MIC and antibacterial effect for *K. pneumoniae* at 24 h

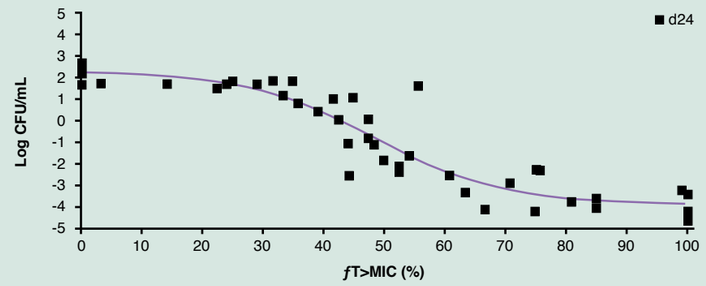


Figure 2. Relationship between *ƒ*T>MIC and antibacterial effect for *E. coli* at 24 h

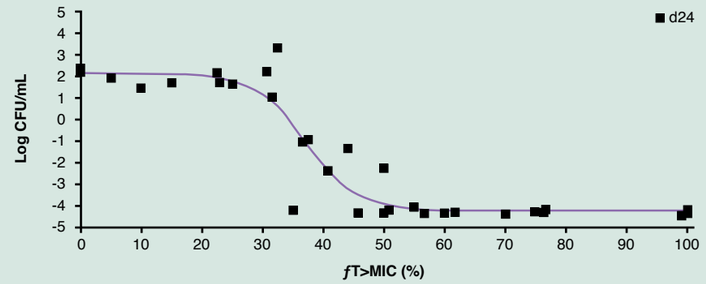
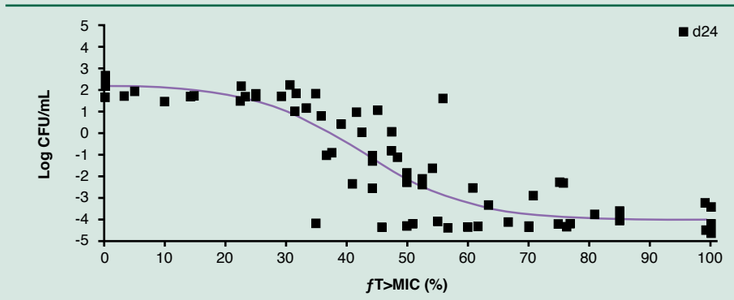


Figure 3. Relationship between *ƒ*T>MIC and antibacterial effect for all strains combined at 24 h



- At a *ƒ*T>MIC of >30–40%, 73% of experiments had growth on x2 MIC plates and 45% of experiments on x4 MIC plates and 9% on x8 MIC plates.
- At a *ƒ*T>MIC >60% no growth was observed on any of the recovery plates.

Conclusions

- A ceftaroline *ƒ*T>MIC of 30–40% is associated with a static to -1 log drop in viable count; this is comparable with other cephalosporins.
- No significant differences were noted in the *ƒ*T>MIC targets for *E. coli* and *K. pneumoniae*.
- It appears that a *ƒ*T>MIC of 60% is required to suppress changes in population profiles at 24 h.

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