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Pharmacodynamics of Ceftaroline Plus Avibactam Against Enterobacteriaceae Studied in an *In Vitro* Pharmacokinetic Model of Infection

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Abstract

Background: The pharmacodynamics (PD) of β-lactam-β-lactamase inhibitor combinations is relatively poorly studied, in terms of both the drug exposures and how frequently drugs should be given to optimise antibacterial effect. We tested a combination of CPT + avibactam (AVI; previously NXL104) against representative strains of Enterobacteriaceae giving CPT 8hly or 12hly and AVI 8hly, 12hly or 24hly.

Methods: A dilutional in vitro pharmacokinetic model was used with three Enterobacteriaceae strains; *E. coli* (CTX-M +) CPT/AVI MIC 0.08mg/L; *Enterobacter cloacae* (AmpC +) CPT/AVI MIC 1.8mg/L; *K. pneumoniae* (KPC +) CPT/AVI MIC 3.0mg/L. Experiments were conducted at an inoculum of 10^6CFU/ml, in triplicate over 96hr. CPT simulations were 600mg 8hly or 12hly and AVI of 600mg 8hly or 12hly and 1200mg or 1800mg 24hly.

Results: Log reduction in viable count (log CFU/ml) at 24h (d24) and 96h (d96) for the various regimens against the strain tested are shown below (mean ± SD):

	E. coli CTX-M		*E. cloacae* AmpC		*K. pneumoniae* KPC	
	d24	d96	d24	d96	d24	d96
CPT 600mg 8hly+AVI 600mg 8hly	-3.7±0.6	-4.0±0.1	-3.6±0.7	-2.0±1.2	-3.1±1.2	-1.2±0.8
CPT 600mg 8hly+AVI 1800mg 24hly	-4.3±0.3	-4.4±0.1	-3.0±0.4	-2.1±0.2	-1.5±0.3	+0.3±0.6
CPT 600mg 12hly+AVI 600mg 12hly	-4.1±0.1	-4.0±0.1	-2.6±0.5	-0.8±0.4	-1.7±0.7	+0.2±1.2
CPT 600mg 12hly+AVI 1200mg 24hly	-2.2±1.3	-1.6±0.7*	-0.8±0.4*	+1.1±0.1*	-0.9±0.6	-0.1±1.3

*24hly inferior to 12hly AVI.

Conclusion: Administration of AVI as a single daily dose was either equivalent, or inferior, to multiple daily dosing. These data favour the administration of AVI in multiple daily doses.

Introduction

- Ceftaroline (CPT), the active component of the prodrug ceftaroline fosamil, is a broad-spectrum cephalosporin with in vitro activity against resistant Gram-positive and ceftazidime-susceptible *Enterobacteriaceae.*
- Avibactam (AVI), previously NXL104, is an investigational non-β-lactam β-lactamase inhibitor with very limited intrinsic antibacterial activity, but efficiently protects β-lactams against Class A, C and some D β-lactamases.
- The combination of CPT plus AVI is currently in phase 2 clinical development.
- The pharmacodynamics of non-β-lactam β-lactamase inhibitor combinations is poorly understood, yet vital to determining optimal dosing regimens.
- We performed dose fractionation studies with CPT plus AVI in order to explore the optimal AVI dose frequency.

Materials

Pharmacokinetics

- Several dosing regimens were employed:

  CPT 600mg twice daily (BD) plus AVI 600mg BD
  CPT 600mg BD plus AVI 1200mg once daily (OD)
  CPT 600mg three times daily (TDS) plus AVI 600mg TDS
  CPT 600mg TDS plus AVI 1800mg OD

- The CPT 600mg simulations produced C_{max} 27 mg/L, t½ 2h, and the AVI 600mg C_{max} 25 mg/L, t½ 2h.
- Simulations were performed over 96h.

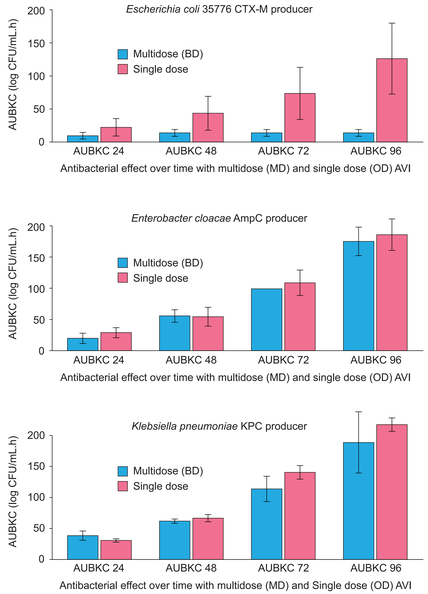
Strain Used

- 3 strains were used – *Escherichia coli* SMD 35576 (CTX-M-15 producer CPT + 2 mg/L AVI, MIC 0.08 mg/L); *Enterobacter cloacae* SMD 42424 (AmpC hyperproducer [derepressed] CPT + 2 mg/L AVI, MIC 1.8 mg/L); *Klebsiella pneumoniae* SMD 42421 (KPC-2 producer CPT + 2 mg/L AVI, MIC 3 mg/L).
- The inoculum was 10^6 CFU/ml and all simulations were performed in triplicate.
- Aliquots were taken throughout the simulations for determination of viable counts by plating onto nutrient agar plates; confirmation of CPT concentration was performed by high-performance liquid chromatography.
- Antibacterial effect was measured by log change in viable counts at 24h, 48h, 72h and 96h (d24, d48, d72, d96) and the area under the bacterial kill curve (AUBKC) at 24h, 48h, 72h and 96h (AUBKC 24h, AUBKC 48h, AUBKC 72h, AUBKC 96h, log CFU/ml.h).
- Antibacterial effects were compared at 24h and 96h by ANOVA.

Results

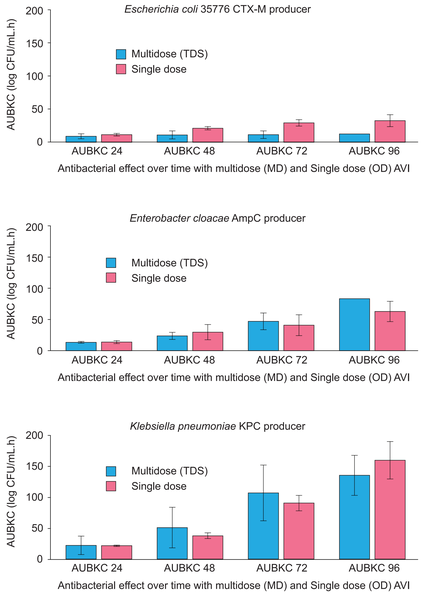
- The comparisons of the log change in viable count at 24h, 48h, 72h and 96h with once-a-day or multidose AVI for all three strains of *Enterobacteriaceae* are shown in Table 1. As reported previously, TDS regimens are superior to BD regimens, most notably with the AmpC-hyperproducing strain and the KPC-producing strain.
- Log change in viable count generally decreased comparably for BD and TDS dosing regimens for *E. coli*, even at 96h (Table 1). In contrast, it appears TDS dosing resulted in higher log change in viable count for *Enterobacteriaceae* up to 96h. No definitive trend was observed for *K. pneumoniae*.
- CPT 600mg BD + AVI 600mg BD was superior to CPT 600mg BD + AVI 1200mg OD for the *E. coli* CTX-M producer at 96h, and the *E. cloacae* AmpC-hyperproducer at 24h and 96h (ANOVA p<0.05). This was not true for the KPC-producing strain.
- CPT 600mg TDS + AVI 600mg TDS was superior to CPT 600mg TDS + AVI 1800mg OD for the KPC-producing strain at 96h. This was not true for the *E. coli* CTX-M producer or the *E. cloacae* AmpC-hyperproducer for any time points.
- The comparison of all the strains of *Enterobacteriaceae* AUBKC at 24h, 48h, 72h and 96h are shown on Figures 1 and 2.
  - AUBKC is substantially higher at all time points for the OD regimen compared with the BD regimen in the *E. coli* strain, whereas such a trend is not observed for *E. cloacae* or *K. pneumoniae* (Figure 1)
  - AUBKC is comparable between the OD and TDS dosing regimens for all 3 strains (Figure 2)
  - AUBKC demonstrates a greater increase with the OD regimen compared with BD dosing (Figure 1), whereas such a trend is not evident when comparing OD and TDS dosing (Figure 2)
- In none of the comparisons was a once-a-day regimen of AVI superior to its equivalent twice or three times a day.

Figure 1. Comparison of Once-a-Day AVI With Multidose AVI Plus CPT 600mg BD Using AUBKC as the Outcome Measure



AUBKC = area under the bacterial kill curve; AVI = avibactam; BD = twice daily; CPT = ceftaroline; OD = once daily.

Figure 2. Comparison of Once-a-Day AVI With Multidose AVI Plus CPT 600mg TDS Using AUBKC as the Outcome Measure



AUBKC = area under the bacterial kill curve; AVI = avibactam; CPT = ceftaroline; OD = once daily; TDS = three times daily.

Table 1. Comparison of Once-a-Day AVI With Multidose AVI Using Change in Viable Count as the Outcome Measure

Log change in viable count ± SD		Ceftaroline regimen	Ceftaroline 600mg BD		Ceftaroline 600mg TDS	
		AVI regimen	600mg BD AVI	1200mg OD AVI	600mg TDS AVI	1800mg OD AVI
Escherichia coli 35576 (CTX-M) MIC 0.08 mg/L						
at:	24h		-4.1 ± 0.1	-2.2 ± 1.3	-4.1 ± 0.1	-4.3 ± 0.3
	48h		-4.1 ± 0.1	-2.4 ± 1.6	-4.1 ± 0.1	-3.5 ± 0.8
	72h		-4.1 ± 0.1	-2.2 ± 1.1	-4.1 ± 0.1	-4.5 ± 0.1
	96h		-4.1 ± 0.1	-1.6 ± 0.7	-4.1 ± 0.1	-4.4 ± 0.1
Enterobacter spp. 42424 (AmpC) MIC 1.8 mg/L						
at:	24h		-2.6 ± 0.5	-2.2 ± 0.1	-3.6 ± 0.7	-3.0 ± 0.4
	48h		1.8 ± 0.3	-1.5 ± 0.7	-3.2 ± 0.3	-3.3 ± 0.8
	72h		1.8 ± 0.4	-1.2 ± 0.1	-2.6 ± 0.3	-3.4 ± 0.6
	96h		0.8 ± 0.4	+1.1 ± 0.1	-2.0 ± 1.2	-2.1 ± 0.2
Klebsiella pneumoniae 42421 (KPC) MIC 3 mg/L						
at:	24h		-1.7 ± 0.7	-0.9 ± 0.6	-3.1 ± 1.2	-1.5 ± 0.3
	48h		-2.3 ± 0.6	-0.6 ± 0.4	-3.0 ± 0.4	-2.0 ± 0.7
	72h		-1.3 ± 1.1	-0.6 ± 0.8	-1.1 ± 1.3	-1.2 ± 0.6
	96h		+0.2 ± 1.2	-0.1 ± 1.3	-1.2 ± 0.8	+0.3 ± 0.6

AVI = avibactam; BD = twice daily; OD = once daily; TDS = three times daily.

Conclusions

- Single daily dosing (OD) AVI is often as effective against *Enterobacteriaceae* producing extended-spectrum β-lactamase (ESBLs), AmpC or KPC enzymes as multidosing (BD or TDS).
- However, there are clear examples when multidosing is superior to OD AVI – especially with the CTX-M-producing strain.
- AUBKC results for TDS dosing generally are comparable with OD dosing at 96h, whereas BD dosing appears to result in lower AUBKC than OD dosing.
- Overall, these data support the administration of AVI TDS or BD compared to OD.

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