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The Pharmacodynamics of Avibactam in Combination With Either Ceftaroline or Ceftazidime Against β-Lactamase-Producing *Enterobacteriaceae*

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Abstract

Background

Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that is paired with ceftaroline fosamil (CPT-F) or ceftazidime (CAZ) in clinical development. AVI inhibits Class A, C, and some D β-lactamases including ESBL, AmpC hyper-producers, and KPC enzymes. The pharmacodynamics of AVI concentration-time-courses in combination with CPT-F or CAZ remains a subject of research. The objective of this study was to delineate the AVI exposure response relationship in combination with standard doses of CPT-F and CAZ against three β-lactamase-producing strains.

Methods

A dilutional single compartment pharmacokinetic model was used to simulate human serum concentrations associated with CPT-F 600 mg q8h and CAZ 2000 mg q8h. AVI was administered by continuous infusion at 0.5, 1, 2, 4, 6, 8, and 10 mg/L. Three strains of *Enterobacteriaceae* were used: *E. coli* CTX-M-15, *E. cloacae* Amp C, and *K. pneumoniae* KPC producer (CPT-F/CAZ MICs 0.12/0.38; 1.8/0.5 and 2/4.5 mg/L with AVI 2 mg/L). The inoculum was 10^6 CFU/mL and the simulations were performed over 72 h. Antibacterial effect was measured by area-under-the-bacterial-kill-curve (AUBKC) and log change in viable count.

Results

Enzyme/ strain	Agent	AVI concentration (mg/L) by continuous infusion for maximum effect at - 24 h	48 h	72 h
CTX-M/ *E. coli*	CPT	0.5-1.0	0.5-1.0	0.5-1.0
	CAZ	0.5-1.0	2.0	2.0
AmpC/ *E. cloacae*	CPT	1.0	1.0-2.0	1.0-2.0
	CAZ	0.5-1.0	1.0-2.0	2.0
KPC/ *K. pneumoniae*	CPT	2.0-4.0	4.0	4.0-6.0
	CAZ	2.0-4.0	2.0-4.0	4.0-6.0

The maximum killing effect was 2-4 logs with the CTX-M producer, 1-3 logs with the AmpC strain, and 2-3 logs with the KPC strain. Killing was less at 72 h than 24 h in most simulations.

Conclusions

AVI by continuous infusion at concentrations of ≥2 mg/L (AUC24 48 mg/L.h) in combination with CPT-F or CAZ is sufficient for a maximum effect against *Enterobacteriaceae* with CTX-M or AmpC enzymes; AVI at a concentration of ≥4 mg/L (AUC24 96 mg/L.h) has a similar effect against the KPC producer. Such AVI exposures are achieved by AVI dosing at doses of 500 mg or 600 mg q8h or q12h.

Introduction

- Avibactam (AVI; previously known as NXL104) is a non-β-lactam, β-lactamase inhibitor with in vitro activity against Class A and Class C and some Class D β-lactamases. In drug development AVI has been paired with 2 different cephalosporins – ceftazidime (CAZ) and ceftaroline (CPT) fosamil, prodrug of the active metabolite, CPT
- The pharmacodynamics of β-lactam-β-lactamase inhibitor combinations are poorly understood compared to β-lactams used as monotherapy
- In particular it is not established how the pharmacodynamic efficacies of various β-lactamase inhibitor exposures are influenced by bacterial species, bacterial strain, specific β-lactamase or β-lactamases present, quantity of β-lactamase produced, or the β-lactam agent with which the inhibitor is paired.

Objective

- We used an in vitro pharmacokinetic model of infection to compare the amount of AVI required to suppress bacterial growth with 3 representative *Enterobacteriaceae*: *E. coli* CTX-M-15 producer, *E. cloacae* AmpC hyperproducer, and *K. pneumoniae* KPC producer.

Materials and Methods

- A dilutional in vitro pharmacokinetic model was used to simulate mean free-drug human serum concentration associated with doses of CPT fosamil 600 mg q8h and CAZ 2000 mg q8h over a period of 72 h. AVI was administered by continuous infusion at concentrations of 0.5, 1, 2, 4, 6, 8, and 10 mg/L
- 3 strains of *Enterobacteriaceae* were used: *E. coli* CTX-M-15 producer, *E. cloacae* AmpC hyperproducer, *K. pneumoniae* KPC producer. The CPT and CAZ MICs with 2 mg/L AVI were:

	MIC (mg/L) Ceftaroline+AVI	Ceftazidime+AVI
E. coli (CTX-M-15)	0.12	0.38
E. cloacae (AmpC)	1.8	0.5
K. pneumoniae (KPC)	2.0	4.5

- The inoculum was 10^6 CFU/mL
- Antibacterial effect was measured by log change in viable count at 24 h, 48 h, and 72 h compared to the inoculum and the area-under-the bacterial kill curve up to 24 h (AUBKC24, log CFU/mL.h), up to 48 h (AUBKC48, log CFU/mL.h), and 72 h (AUBKC72, log CFU/mL.h)
- Concentrations of CPT and CAZ were measured by high-performance liquid chromatography (HPLC).

Results

- The measured concentrations of CPT and CAZ compared to target are shown in Table 1
- The relationships between AVI concentration and antibacterial effect of CPT or CAZ using log change in viable count over 24, 48, and 72 h for *E. coli* (CTX-M-15), *E. cloacae* (AmpC), and *K. pneumoniae* (KPC) are shown in Figures 1-3 for CPT and Figures 4-6 for CAZ
- Antibacterial effect was measured using AUBKC, as shown in Figures 7-9 for CPT and Figures 10-12 for CAZ
- With CPT plus AVI against the CTX-M-15-producing *E. coli*, maximum effect was observed at 1 mg/L AVI, the equivalent values for the AmpC-producing *E. cloacae* and KPC-producing *K. pneumoniae* were 2 and 6 mg/L, respectively
- With CAZ plus AVI against the CTX-M-15-producing *E. coli*, maximum effect was observed at 1 mg/L AVI, the equivalent values for the AmpC-producing *E. cloacae* and KPC-producing *K. pneumoniae* were 4 and 6 mg/L, respectively
- For the *E. coli* CTX-M-15, the maximum effect occurred at 1 mg/L for both CPT and CAZ; for the *E. cloacae* AmpC higher producer, the maximum effect occurred at 1 mg/L for CPT and CAZ, whereas for the *K. pneumoniae* KPC producer, the maximum effect occurred at 4-6 mg/L for CPT and 2-4 mg/L for CAZ
- With both cephalosporins and all 3 bacterial strains, there was a tendency for the antibacterial effect to be greater at 24 h than at 72 h.

Figure 1. Ceftaroline Antibacterial Effect Against CTX-M-15-Producing *E. coli* in the Presence of Increasing Concentrations of Avibactam

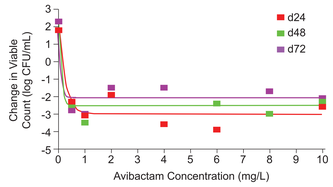

Figure 2. Ceftaroline Antibacterial Effect Against *E. cloacae* (AmpC hyperproducer) in the Presence of Increasing Concentrations of Avibactam

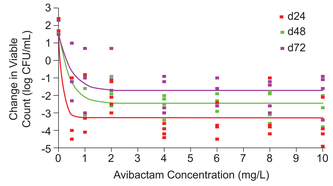

Figure 3. Ceftaroline Antibacterial Effect Against KPC-Producing *K. pneumoniae* in the Presence of Increasing Concentrations of Avibactam

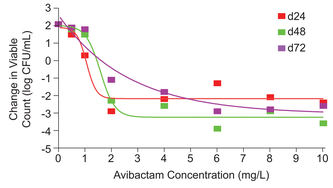

Figure 4. Ceftazidime Antibacterial Effect Against CTX-M-15-Producing *E. coli* in the Presence of Increasing Concentrations of Avibactam

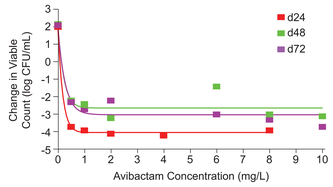

Figure 5. Ceftazidime Antibacterial Effect Against *E. cloacae* (AmpC hyperproducer) in the Presence of Increasing Concentrations of Avibactam

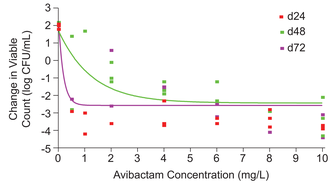

Figure 6. Ceftazidime Antibacterial Effect Against KPC-Producing *K. pneumoniae* in the Presence of Increasing Concentrations of Avibactam

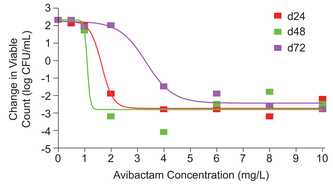

Figure 7. Ceftaroline Antibacterial Effect Against CTX-M-15-Producing *E. coli* in the Presence of Increasing Concentrations of Avibactam

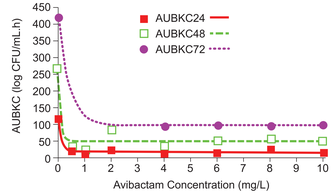

Figure 8. Ceftaroline Antibacterial Effect Against AmpC-Hyperproducing *E. cloacae* in the Presence of Increasing Concentrations of Avibactam

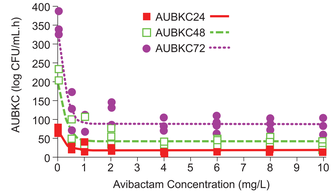

Figure 9. Ceftaroline Antibacterial Effect Against KPC-Producing *K. pneumoniae* in the Presence of Increasing Concentrations of Avibactam

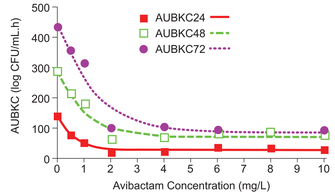

Figure 10. Ceftazidime Antibacterial Effect Against CTX-M-15-Producing *E. coli* in the Presence of Increasing Concentrations of Avibactam

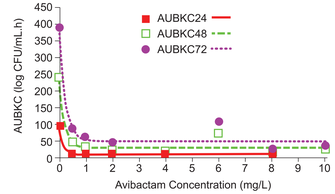

Figure 11. Ceftazidime Antibacterial Effect Against AmpC-Hyperproducing *E. cloacae* in the Presence of Increasing Concentrations of Avibactam

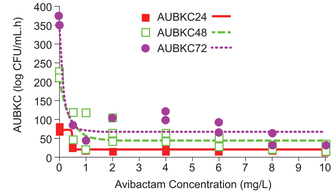

Figure 12. Ceftazidime Antibacterial Effect Against KPC-Producing *K. pneumoniae* in the Presence of Increasing Concentrations of Avibactam

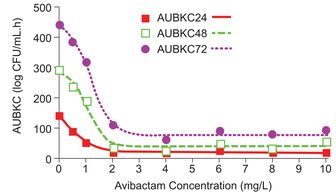

Table 1. Target and Measured Ceftaroline and Ceftazidime Concentrations

Time (h)	Ceftaroline Target (mg/L)	Ceftaroline Measured (mg/L)	Ceftazidime Target (mg/L)	Ceftazidime Measured (mg/L)
0	0	0	0	0
1	27.0	23.8 ± 5.4	23.2	23.8 ± 2.7
2	12.8	13.4 ± 2.9	46.3	42.1 ± 5.1
3	9.4	9.2 ± 3.0	34.7	33.4 ± 2.7
4	6.0	7.1 ± 2.6	23.1	22.7 ± 2.8
5	4.6	5.5 ± 1.7	18.0	17.2 ± 1.7
6	3.2	4.1 ± 1.5	13.0	12.2 ± 1.5
7	2.5	3.1 ± 1.2	10.2	9.5 ± 1.1
8	1.7	2.0 ± 0.7	7.4	6.6 ± 1.1
12	6.0	5.1 ± 0.6	-	-
27	9.4	9.9 ± 0.6	-	-
28	6.0	6.1 ± 0.4	23.1	22.2 ± 0.6

Conclusions

- AVI at concentrations of ≥2 mg/L (AUC24, 48 mg/L.h) in combination with CPT or CAZ was sufficient for maximum effect against representative strains of *E. coli* producing CTX-M-15 enzyme or hyper AmpC-producing *E. cloacae*
- AVI at concentrations of ≥4 mg/L was required to have similar effects against KPC-producing *K. pneumoniae* (AUC24, 96 mg/L.h)
- There were no clear differences in terms of antibacterial effect of AVI when combined with either CPT or CAZ
- AVI 24 h exposures of up to 96 mg/L.h can be achieved in humans with doses of 500 mg or 600 mg q8h or q12h.

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