ICAAC 2011
A2-556

Pharmacodynamics of Avibactam Plus Either Ceftaroline or Ceftazidime Against an AmpC-Producing *Enterobacter* spp.

K.E. Bowker,[1] A.R. Noel,[1] A.P. MacGowan,[1] G. Williams[2]

[1]Bristol Centre for Antimicrobial Research & Evaluation (BCARE) North Bristol NHS Trust & University of Bristol, Bristol, United Kingdom; [2]Cerexa, Inc., Oakland, California (a wholly owned subsidiary of Forest Laboratories, Inc., New York, New York)

BCARE
Department of Medical Microbiology
Lime Walk Building
Southmead Hospital
Westbury-on-Trym
Bristol
BS10 5NB United Kingdom
Tel: +44 (0) 117 323 5601/4187
Fax: +44 (0) 117 323 8332
E-mail: karen.bowker@nbt.nhs.uk

Amended Abstract

Background: Avibactam, previously NXL104 (AVI), is a non-β-lactam β-lactamase inhibitor which has been combined with ceftaroline (CPT) or ceftazidime (CAZ) in pre-clinical and/or clinical studies. The amount of AVI required to inhibit common β-lactamases when these cephalosporins are given at human doses is not established. We used an in vitro pharmacokinetic (PK) model to simulate standard doses of CPT or CAZ combined with increasing exposures of AVI given as a continuous infusion.

Methods: A single compartment dilutional PK in vitro model was used to simulate serum concentrations of CPT associated with 600 mg 8hly (C_{max} 27.1 mg/L, $t_{½}$ 2.5h) or CAZ 2000 mg 8hly (C_{max} 46 mg/L, $t_{½}$ 2h) over 48h. AVI was given by continuous infusion at 2, 4, 6, 8 or 10 mg/L. *Enterobacter cloacae* (AmpC+) at an inoculum of 10^6 CFU/mL was the target pathogen. Dose response curves were developed for AVI with CPT and CAZ.

Results: In the absence of AVI *Ent.cloacae* viable counts increased to 10^8 CFU/mL by 24h with both CPT and CAZ. Addition of ≥1 mg/L AVI significantly increased the antibacterial effect of both cephalosporins. At 24h with CPT and CAZ, ≥1 mg/L AVI reduced counts by ≥2 logs. At 48h exposure 1-2 mg/L AVI + CPT or CAZ produced ≥2 log reductions in bacterial counts. The maximum effect at 48h of AVI was 1-2 mg/L with AVI + CPT and with AVI + CAZ.

Conclusions: AVI + CPT or CAZ behave in similar ways against an AmpC producing *Ent. cloacae* spp. AVI 1-2 mg/L was associated with maximum effect at 24h, 48h and 72h.

Introduction

- Avibactam (AVI), previously NXL104, is a non-β-lactam β-lactamase inhibitor with very limited intrinsic antibacterial activity, but efficiently protects β-lactams against Class A, Class C and some Class D β-lactamases.
- AVI is paired with two different cephalosporins in clinical development: ceftaroline (CPT) and ceftazidime (CAZ).
- It is not clear how much AVI should be combined with each cephalosporin to enhance the antibacterial effects against β-lactamase-producing *Enterobacteriaceae* and whether the optimal amounts of AVI would differ for the two cephalosporins.
- We used a dilutional in vitro pharmacokinetic model to simulate the human serum concentrations of CPT or CAZ observed with standard doses combined with the addition of increasing concentrations of AVI at a variety of continuous infusion levels.

Materials and Methods

Pharmacokinetics

- CPT 600 mg three times a day (TDS), C_{max} 27.1 mg/L, $t_{½}$ 2h for 72h
- CAZ 2000 mg TDS, C_{max} 46.3 mg/L, $t_{½}$ 2h for 72h
- AVI administered as a continuous infusion at 0, 0.5, 1, 2, 4, 6, 8, 10 mg/L for 72h using Mueller Hinton Broth.

Strain Used

A single strain of AmpC-hyperproducing *Enterobacter cloacae* 42424 with a CPT + 2 mg/L AVI MIC of 1.8 mg/L and a CAZ + 2 mg/L AVI MIC of 0.5 mg/L was used.

The inoculum employed was 10^6 CFU/mL.

Aliquots were taken throughout the dosing intervals for viable counts on nutrient agar plates and for confirmation of CPT and CAZ concentrations using high-performance liquid chromatography.

Antibacterial effect was measured by log change in viable counts at 24, 48 and 72 hours (d24, d48, d72) and area under the bacterial kill curve at 24, 48 and 72 hours (AUBKC 24, AUBKC 48, AUBKC 72).

The relationship between antibacterial effect (log drop in viable count or AUBKC) and AVI concentration was explored using a sigmoid E_{max} model using Boltzmann's Equation.

Results

Figure 1. Time Kill Curves - Ceftaroline + AVI

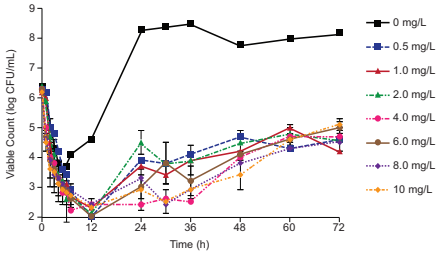


Figure 2. Time Kill Curves - Ceftazidime + AVI

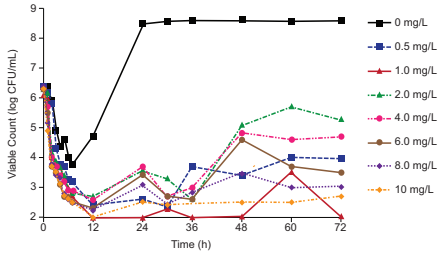


Figure 3a and b. Relationship Between AVI Concentration and Antibacterial Effect Measured by Change in Viable Count at 24, 48 and 72h

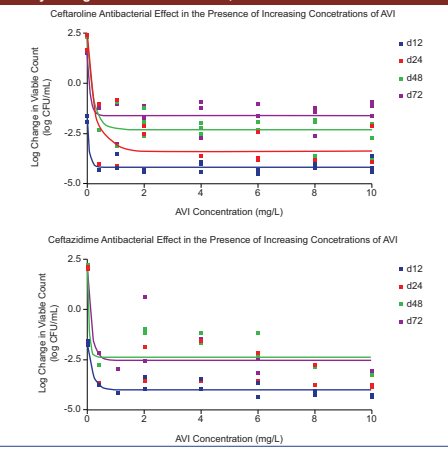
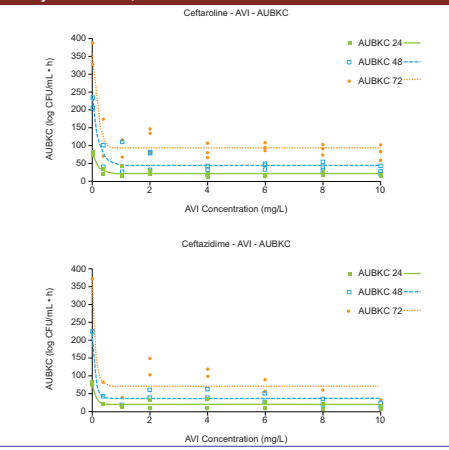


Figure 4a and b. Relationship Between AVI Concentration and Antibacterial Effect Measured by AUBKC at 24, 48 and 72h



- The time kill curves for CPT or CAZ plus AVI are shown on Figures 1 and 2. For CPT and CAZ without AVI, there was a 2-3 log kill by 6h followed by regrowth to 10^8 CFU/mL at 24hr.
- For CPT and CAZ plus AVI, there was 4 log kill by 12h followed by some regrowth up to 72h. With CPT plus AVI, the final bacterial density was 4-5 $\log_{10}$ CFU/mL. With CAZ, there was regrowth to 2-5.5 log CFU/mL at 72h and there appeared to be more experimental variability with CAZ than CPT.
- The relationship between AVI continuous concentration and antibacterial effect for CPT and CAZ using log drop in count (Figures 3a and 3b) and AUBKC (Figures 4a and 4b) are shown. Sigmoid curve fit was satisfactory (R^2 0.67 – 0.99).
- With both CPT or CAZ and either antibacterial effect endpoint (log drop or AUBKC), the greatest AVI effect occurred up to 1-2 mg/L. Increasing the AVI concentration >2 mg/L did not appear to further increase kill as defined by this analytical approach.
- Of note, the maximum AVI effect decreased as time increased – this is a direct result of regrowth as illustrated on Figures 1 and 2. Hence, AVI had a greater effect at 24h than 48h or 72hr. The greater variability in the CAZ experiments, compared to CPT, is also illustrated in Figures 3a and 3b.

Conclusions

- Continuous infusion AVI resulted in a marked increase in the antibacterial effect of both CPT and CAZ against this AmpC hyperproducing *Ent.cloacae*.
- Using this model and analytical approach, the maximum effect of AVI is seen at 1-2 mg/L with both CPT and CAZ in the first 12-24h of exposure.
- The concentration of AVI required is likely to be conditional on the type of β-lactamase, its level of production, other resistance mechanisms present, and perhaps the bacterial species and strain. High inoculum is likely to increase the amount of AVI required for a chosen effect and results may vary with different PK/PD models.

Acknowledgments

This study was supported by Cerexa, Inc., a wholly owned subsidiary of Forest Laboratories, Inc. Cerexa, Inc. was involved in the design of the study and the decision to present these results. Cerexa, Inc. had no involvement in the collection, analysis, and interpretation of data. Scientific Therapeutics Information, Inc. provided editorial coordination and production services, which were funded by Forest Research Institute, Inc.