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 understood. We examined a combination of CPT + avibactam (AVI) (previously NXL104) against representative strains of Enterobacteriaceae using CPT 8hly and 12hly and AVI 600mg or 1200mg 24hly.

Materials

Pharmacokinetics

Several dosing regimens were employed:

- CPT 600mg 8hly + AVI 600mg 8hly
- CPT 600mg 8hly + AVI 1200mg 24hly
- CPT 600mg 12hly + AVI 600mg 12hly
- CPT 600mg 12hly + AVI 1800mg 24hly

- The CPT 600mg 8hly + AVI 600mg 8hly regimen was superior to CPT 600mg BD + AVI 600mg OD for the E. coli AmpC producer and the E. coli AmpC hyperproducer at 24h and 96h (ANOVA p<0.05).

- 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 CPT dosing (Figure 1), whereas such a trend is not evident when comparing CPT and TDS dosing (Figure 2).

- The comparison of all the strains of Enterobacteriaceae AUBKC at 24h, 48h, 72h and 96h with once-a-day or multidose AVI for all three Enterobacteriaceae strains is shown in Figure 1 (A).

- AUBKC is substantially higher at all time points for the OD regimen compared with the BD regimen for all Enterobacteriaceae strains.

- In all cases the comparison was a once-a-day regimen of AVI superior to the equivalent twice or thrice-a-day dosing.

- Microbiological: 3 strains were used: E. coli, Enterococcus faecalis, and Enterobacter cloacae. Each strain was tested for MIC and AUBKC. The MIC and AUBKC values were compared with and without AVI.

- Simulations were performed for 96h.

- The inoculum was 10² CFU/mL and all simulations were performed in triplicate.

- Aliquots were taken throughout the simulations for determination of viable count and AUBKC. The area under the bacterial kill curve (AUBKC) was calculated.

- Antibacterial effect was measured as log change in viable count for all time points.

Introduction

• CPT, the active component of the produg ceftaroline fosamil, is a broad-spectrum cephalosporin with in vitro activity against Gram-positive and certain Gram-negative 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 and C 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 are understudied, yet difficult to determine due to poor PK.

• We performed dose fractionation studies with CPT plus AVI in order to explore the optimal AVI time frame.

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 AmpC-hyperproducer at 72h and 96h (ANOVA p<0.05).

• Log change in viable count generally decreased comparably for BD and TDS dosing regimens for E. coli and K. pneumoniae (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 OD + AVI 1200mg OD for the E. coli AmpC producer at 96h, and the E. coli AmpC producer at 96h and K. pneumoniae at 72h.

• This was not true for the KPC-producing strain.

• CPT 600mg TDS + AVI 600mg TDS was superior to CPT 600mg OD for the KPC-producing strain at 96h. This was not true for the E. coli CTX-M producer of the E. coli AmpC producer for any time points.

• The comparison of all the strains of Enterobacteriaceae AUBKC at 24h, 48h, 72h and 96h with once-a-day or multidose AVI for all three Enterobacteriaceae strains is shown in Figure 1 (A).

• AUBKC demonstrates a greater increase with the OD regimen compared with CPT dosing (Figure 1), whereas such a trend is not evident when comparing CPT and TDS dosing (Figure 2).

• In all cases the comparison was a once-a-day regimen of AVI superior to the equivalent twice or thrice-a-day dosing.

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Conclusions

- Single daily dosing (OD) AVI is often as effective against Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL), 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 those of CPT 600mg OD; however, this result appears in lower AUBKC than CPT OD dosing.

- A UBIC is a single administration of AVI compared to the administration of AVI TDS or OD compared to CPT OD.

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