The pharmacodynamics of Avibactam in combination with either Cefotaxime or Ceftazidime against β-Lactamase-producing Enterobacteriaceae

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Introduction

Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that is paired with ceftazidime (CAZ) or ceftazidime fosamil (CPT) in vitro. Microbiological and pharmacokinetic studies have shown AVI to be active with selected β-lactamase producing strains of K. pneumoniae and E. coli (KPC) and E. cloacae (AmpC), respectively. AVI is available for use as a monotherapy or in combination with CAZ.

Materials and Methods

A biofilm containing strain of K. pneumoniae and E. cloacae was used to measure the difference in viable count over 24, 48, and 72 h for CAZ 2000 mg q8h over a period of 72 h. 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 CPT, and K. pneumoniae/CAZ fosamil (CPT-CAZ-MICs 0.12/0.38; 1.8/0.5 and 2/4.5 mg/L). The inoculum was 10^5 CFU/mL, and the simulations were performed over 72 h. Antibacterial effect was measured by inoculum-based pharmacodynamics (AUBKC) and log change in viable count.

Avibactam (AVI) is a non-β-lactam, β-lactamase inhibitor with in vitro activity against ESBL, AmpC hyper-producers, and KPC enzymes. The pharmacodynamics of AVI concentration-time courses in combination with CPT or CAZ are subjects of research. The objective of this study was to delineate the AVI exposure-response relationship at the standard doses of CPT and CAZ against these β-lactamase-producing strains.

Methods

A dual component pharmacokinetic-pharmacodynamic model was used to simulate the human serum concentrations of AVI and CAZ from 2 mg/L. The inoculum was 10^5 CFU/mL, and the simulations were performed over 72 h. Antibacterial effect was measured by inoculum-based pharmacodynamics (AUBKC) and log change in viable count.

Results

Avibactam (AVI) concentrations (mg/L) by continuous infusion for maximum effect at -

M-15-Producing

Enterobacteriaceae

Carbapenem producer, 1-3 logs with the AmpC strain, and 2-3 logs

KPC/Enterobacteriaceae strain

Avibactam was measured using AUBKC, as shown in Figure 5 for CAZ and Figures 8-10 for CAZ. 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 strain, the maximum effect was observed at 1 mg/L for both CPT and CAZ for the K. pneumoniae AmpC 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 CAZ and 2-4 mg/L for CAZ.

Conclusion

With both cephalosporins and 4-6 lactic acid there was a tendency for the antibacterial effect to be greater at 24 h than at 72 h.

Table 1. Target and Measured Ceftazidime and Ceftazidime Fosamil Concentrations

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Target (mg/L)</th>
<th>Measured (mg/L)</th>
<th>Measured (mg/L)</th>
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<tbody>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>72</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
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</table>

Conclusions

AVI 24 h exposures of up to 96 mg/L.h can be achieved in combination with either CAZ or CPT.

Acknowledgments

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