In Vitro Activity of Ceftazidime-Avibactam (CAZ-AVI) and Comparators Against Gram-negative Pathogens

Isolated from Patients in Canadian Hospitals in 2009-2014: CANWARD Surveillance Study

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ABSTRACT

Background: Avibactam, a β-lactamase inhibitor of Ambler class A-C and some class D enzymes in combination with ceftazidime, is FDA approved for the treatment of complicated urinary tract and intra-abdominal infections in adults. We determined the in vitro activity of ceftazidime (CAZ) with avibactam (fixed 4 μg/mL concentration) and compared it to various Gram-negative pathogens, including a broad-spectrum β-lactamase producing (ESBL) and AmpC-producing (AmpC) Enterobacteriaceae and Pseudomonas aeruginosa. Resistance patterns were generated using fractional inhibitory concentration (MIC) breakpoints distributed worldwide, intensive care units, clinics, and emergency rooms at 15 Canadian hospitals.

Methods: Antimicrobial susceptibility testing was performed using broth microdilution plates following CLSI recommendations (M07-A10). Susceptibility was defined in accordance with CLSI, except for CAZ-AVI, where the FDA breakpoints were used. Ceftazidime-resistant Enterobacteriaceae and Klebsiella spp. isolates were genetically characterized for ESBL production using PCR and sequence analysis.

Results: The activity of CAZ-AVI and comparators is summarized in Table 1 and 2.

Conclusions: CAZ-AVI demonstrated potent in vitro activity against recent clinical isolates of enteric pathogens including those with ESBL producing and Amp C β-lactamase producing bacteria. These results were achieved with a variety of mechanisms, MICs of CAZ-AVI against P. aeruginosa were comparable to meropenem; however, it had lower than CAZ alone. CAZ-AVI was most active against some Enterobacteriaceae, M. tuberculosis and TET-resistant P. aeruginosa. Activity against A. baumannii was not improved compared to CAZ alone. Activity against ESBL-producing strains were somewhat better than CAZ alone. CAZ-AVI may be useful for the treatment of infections caused by β-lactam-resistant Enterobacteriaceae.

BACKGROUND

Antimicrobial resistance is a growing problem among Gram-negative isolates worldwide. Multi-drug-resistant (MDR) P. aeruginosa, KLE- and AmpC-producing Enteroberacteriaceae, and MDR Acinetobacter spp. can cause severe infection and treatment choices are limited. A broad-spectrum non-β-lactam β-lactamase inhibitor being studied in combination with ceftazidime to restore the parent drug activity against a wide range of carbapenem-resistant Gram-negative pathogens expressing Ambler class A and C, and some class D β-lactamases (1)

MATERIALS & METHODS

Isolates were collected as part of the CANWARD 2009 through to CANWARDS 2014 surveillance study, comparing between January 2009 and October 2014. 15 Canadian centers provided 15315 isolates distributed worldwide. A total of 16896 isolates from the 15 Canadian centers were included. Susceptibility testing was done by broth microdilution in accordance with the CLSI document M07-A10 (2). Serial dilutions of ceftazidime with and without a fixed concentration of 4 μg/mL avibactam, piperacillin-tazobactam, ceftazidime, and meropenem and tazobactam were performed in accordance with CLSI guidelines. The MIC was defined in accordance with CLSI, except for CAZ-AVI, where the FDA breakpoints were used. Ceftazidime-resistant Escherichia coli and Klebsiella spp. isolates were genetically characterized for ESBL producing using PCR and sequence analysis.

RESULTS

Table 1: MICs and MIC50 for all isolates and cephalosporin-resistant isolates for ceftazidime-avibactam and comparators.

Table 2: Percent susceptible for all isolates and cephalosporin-resistant isolates to ceftazidime-avibactam and comparators.

CONCLUSIONS

Avibactam reduced MIC50 and MIC90 of ceftazidime for all organisms tested except A. baumannii and S. maltophilia. Avibactam restored the activity of ceftazidime for all Enterobacteriaceae with acquired resistance to ceftriaxone.

Avibactam resulted in a 2-fold reduction in MIC50 and 4-fold reduction in MIC90 compared with ceftazidime alone for P. aeruginosa.

Ceftazidime-avibactam susceptibility rates are >99% for all Enterobacteriaceae (77.8 – 99.2% for ceftazidime alone), 94.4% for P. aeruginosa (82.5% for ceftazidime alone) and 61.5% (using the ceftazidime breakpoint) for A. baumannii (78.9% for ceftazidime alone). Ceftazidime-avibactam susceptibility rates are comparable with meropenem for Enterobacteriaceae, superior to meropenem for P. aeruginosa.

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