Antimicrobial Activity of Ceftolozane Combined With NXL104 Tested Against a Collection of Organisms Expressing Multiple β-Lactamases

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Materials and Methods

Background Information

A total of 148 β-lactamase-producing Enterobacteriaceae strains (identified using the 2012 CLSI protocol) were collected from the 2010 Canadian Antimicrobial Surveillance Program (CASP) and other international programs. Enterobacteriaceae strains were collected from a variety of sources, including urinary, respiratory, and wound infections. All strains were tested for extended-spectrum β-lactamases and Carba NP (E. coli) or Carba NP (Klebsiella spp.) were identified using the Carba NP test (Blue Rabbit Diagnostics, Oberursel, Germany) as described in the CLSI Methods for detection of extended-spectrum β-lactamases and carbapenemases (M101-A9, 2015). The results of these tests were interpreted in accordance with the CLSI guidelines for laboratories that perform antimicrobial susceptibility testing. All strains were confirmed as Enterobacteriaceae using the API 20E/20NE system (bioMérieux, Marcy l’Etoile, France). The identity of all strains was confirmed by 16S rRNA gene sequencing.

Susceptibility Testing

All strains were tested for antimicrobial susceptibility using the CLSI agar dilution protocol as described in the Clinical and Laboratory Standards Institute (CLSI) guidelines. Bacteria grown on sheep blood agar were suspended in tryptone broth and adjusted to an optical density of 0.125 (A600nm = 0.125). Bacteria were then inoculated onto Mueller-Hinton agar plates and incubated for 16-20 hours at 35°C. After incubation, the plates were coded and sent to the laboratory for testing.

Genotypic Detection of β-Lactamase Genes

Different PCR primers were used to detect different β-lactamase genes. β-Lactamase genes were detected as described elsewhere. Positive results were confirmed by sequencing. Sequencing results were analyzed using the Phred/Phrap/Consed software package (DNA Technologies, Inc., University of Washington, Seattle, WA).

Conclusions

CPT104 demonstrated excellent in vitro activity against these very challenging isolates. CPT104 was highly active against multidrug-resistant β-lactamase-producing Enterobacteriaceae (except MBLs), including isolates producing up to 4 different β-lactamases. In general, collateral MIC reductions were variable, but MIC values were 2-fold to 8-fold lower when NXL104 was combined with cefepime than when cefepime was combined alone for all groups (except MBL-producing strains).

Many β-lactamase groups have been highlighted by the epidemic spread of β-lactamase-producing organisms. New β-lactams with broad-spectrum activity against Gram-negative pathogens have developed. Advances in the treatment of β-lactamase-producing organisms have been made over the past few years. CPT104 was recently approved by the US Food and Drug Administration for the treatment of complicated urinary tract infections (CUTI), complicated diverticulitis (CD), and community-acquired pneumonia (CAP) caused by Enterobacteriaceae and P. aeruginosa. It is a promising therapeutic option for treatment of infections caused by multidrug-resistant Enterobacteriaceae and P. aeruginosa.

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References