Enriched Activity of WCK 4282 (Celmece-Tazobactam) Against KPC-Producing Enterobacteriaceae Collected Worldwide When Tested in Physiological Conditions

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Amended Abstract

Introduction

Since its first description in 2001, Klebsiella pneumoniae carbapenemase (KPC) producing bacteria have been reported for hospital worldwide. This organism has been considered very inflammatory because of its intrinsic resistance across extended-spectrum β-lactamases (ESBL) spp., clinical isolates, but it can also be found among other Enterobacteriaceae species. KPC-producing organisms are usually resistant to virtually all β-lactams and many of the other antifungal classes, limiting the therapeutic options to treat the infections caused by them.

WCK 4282 combines cefepime (FEP) with tazobactam (TAZ) and is currently under clinical development at 24-hg as well as q12 hours dosage. Tazobactam was found to be active against several isolates producing extended-spectrum β-lactamases and AmpC-producing isolates under standard conditions. In order to understand the basis of its in vivo efficacy in neonatal animal models we evaluated the efficacy of cefepime-tazobactam when tested in media simulating physiological conditions (ICAH) against KPC-producing Enterobacteriaceae isolates.

Methods

Bacterial isolates: A total of 210 KPC-producing Enterobacteriaceae clinical isolates collected during 2005-2015 were evaluated. These isolates were from various hospital locations in 16 countries in 60 cities. The results were compared to those obtained for 3 different β-lactam antibiotics: amoxicillin (8 µg/mL), the reference method (Villegas MV, Wang H, Woodford N, Quinn JP (2013). JMI 18: 413-421).

Resistance Testing and other Clinical Characteristics: All strains were confirmed by Matrix-Assisted Laser Desorption Ionization-Time Of Flight Mass Spectrometry (Bruker Daltonics MA DI Biospectra, Billerica, Massachusetts, USA) following manufacturer instructions. PCR encoding genes were screened using PCR methods or a microarray based assay (Check-MDR CT111 Kit; Check-marks, Wageningen, Netherlands). Sequencing was performed and protein alignments were compared with available sequences.

Antimicrobial susceptibility testing: MICs for FEP were determined in two media: Clinical and Laboratory Standards Institute (CLSI) (2015). FEP was tested in 3 media types: Mueller Hinton Broth (MHB), Mueller Hinton Broth with 50% pooled human serum (MHB supplemented with 0.85% NaCl (supplemented with saline or human serum)) and Mueller Hinton Broth supplemented with 0.85% NaCl (MHB supplemented with human serum) or NaCl in (no conditions) and 79.5% of the isolates were inhibited by FEP at ≤16 µg/mL.

Results

KPC-producing Enterobacteriaceae species displayed elevated FEP (MIC50 = 24/54 µg/mL; MIC90 = 6/124 µg/mL; MIC values were ≤16/32 µg/mL for 50% of these isolates) when tested under standard conditions (Table 1). The activity of FEP (MIC50 = 16/54 µg/mL) was similar when tested under standard conditions and 80.5% of the isolates were inhibited by this combination at ≤16 µg/mL (Table 1).

When FEP was tested against KPC-producing Enterobacteriaceae in the 0.85% NaCl supplemented medium, the MIC50 and MIC90 values were ≤8 and 32 µg/mL, respectively (Table 1), when compared to results of testing under standard conditions (CA-MHB) and 80.5% of the isolates were inhibited by FEP at ≤16 µg/mL when tested in MHB supplemented with NaCl.

MIC50 and MIC90 values (≤8 and 32 µg/mL, respectively) for FEP alone were demonstrated for KPC-producing Enterobacteriaceae isolates. In standard conditions (CA-MHB) the activity of FEP against KPC-producing Enterobacteriaceae isolates varied by species, prokaryotic, or carbapenemase (KPC), strain and geographical location. FEP displayed similar activity against KPC-producing Enterobacteriaceae with reference methods (ICAH) and FEP MIC results were two-fold lower when other FEP combinations displayed activity against KPC-producing Enterobacteriaceae isolates.

Conclusion

• FEP zinc tested in CA-MHB supplemented with 0.85% NaCl or 50% serum inhibited 80.5% and 7.95% of the KPC-producing Enterobacteriaceae at 16/54 µg/mL, respectively.

• The limited options to treat multidrug resistant KPC-producing Enterobacteriaceae and the dissemination of these isolates worldwide warrant the further development new antimicrobial agents and combination therapies.

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References


