27th ECCMID Vienna, Austria 22 – 25 April 2017

The congress of ESCMID

Session: P097 Understanding and managing Clostridium difficile

Category: 5a. Mechanisms of action, preclinical data & pharmacology of antibacterial agents

25 April 2017, 12:30 - 13:30
P2047

Time-kill kinetics and post-antibiotic effect of cadazolid against Clostridium difficile

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Background: *Clostridium difficile* infection (CDI) is a leading cause of nosocomial diarrhoea worldwide. The increase over the past decade has been attributed to the emergence of hypervirulent strains including *C. difficile* BI/NAP1/ribotype 027 and BK/NAP7/ribotype 078. Cadazolid is a new antibiotic currently in clinical Phase III studies for the treatment of CDI. Here we determined the *in vitro* time-kill kinetics and post-antibiotic effect (PAE) of cadazolid (CDZ) compared to fidaxomicin (FDX) and vancomycin (VAN) against a panel of 4 *C. difficile* strains from ribotypes 027, 078, 087 and 001.

Material/methods: Anaerobic broth microdilution MICs were determined based on the CLSI guidelines M11-A8 and M100-S26 using brain heart infusion supplemented broth (BHIS) containing 5 g/L yeast extract and 0.025% (w/v) L-cysteine. Time-kill kinetics, to investigate rate of killing of each antibiotic at sub- and supra-MIC concentrations, and PAE experiments, to evaluate the delayed regrowth of strains following 1 h exposure to each antibiotic, were performed at concentrations of 0.5, 1, 2, 4, 8 or 16x the MIC of CDZ, FDX and VAN.

Results: In time kill studies, CDZ was bactericidal against 3 out of 4 *C. difficile* isolates as defined by ≥3 $\log_{10}$ CFU/mL reduction within 24 h, and ≥2 $\log_{10}$ CFU/mL reduction was achieved against all 4 test strains. Notably, CDZ was bactericidal against both hypervirulent strains tested (ribotypes 027 and 078). CDZ killing rates were concentration-dependent in a range of 0.5 to 4x MIC, and were not further enhanced at concentrations >4x MIC in 3 out of 4 strains. Increasing the exposure from 24 h to 48 h only modestly increased the killing efficacy. Overall, the killing effect of CDZ was similar to that of FDX

and superior to VAN. In PAE experiments the recovery kinetics of *C. difficile* isolates exposed to CDZ for 1 h were strain- and concentration-dependent, with prolonged PAEs of >8 h observed against *C. difficile* ATCC 43255 and ATCC BAA 1875, but shorter PAEs of 0 to 2 h were recorded for *C. difficile* ATCC 9689 and NCTC 13366, at all concentrations tested. In comparison VAN showed short PAEs (0-2 h) against all strains and at all test concentrations, while FDX showed long (>8 h) PAEs against three out of four strains.

Conclusions: CDZ mediated killing was faster and occurred at lower concentrations than observed for VAN, while FDX potency and killing was similar. PAEs of CDZ varied depending on strains and test concentration.