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P1672 Evaluation of synergistic effects of a potentiator molecule (SPR741) when tested in combination with a series of beta-lactam agents against a challenge set of Gram-negative pathogens

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Background: *Enterobacteriaceae* can express a diverse array of β-lactam antimicrobial resistance mechanisms, including β-lactamase enzymes, which can compromise therapy. SPR741 is a novel polymyxin B derivative with minimal intrinsic antibacterial activity and reduced nonclinical nephrotoxicity. This study assessed *in vitro* activity of a series of β-lactam agents tested in combination with SPR741 against a challenge set of pathogens.

Materials/methods: A total of 423 bacterial clinical isolates were selected by the presence of β-lactamases, including plasmid AmpC (pAmpC), extended-spectrum β-lactamase (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), metallo-β-lactamase (MBL), and OXA-48-like enzymes. Isolates were tested for susceptibility by CLSI methods for aztreonam, cefepime, cefotaxime, cefoxitin, ceftazidime, mecillinam, meropenem, piperacillin-tazobactam, and temocillin with and without SPR741 at fixed concentration of 8 mg/L. β-lactam MIC results were interpreted based on CLSI/EUCAST/BSAC breakpoints, which were also applied to the combinations for comparison purposes.

Results: Using EUCAST breakpoints, mecillinam-SPR741 provided high susceptibility rates (96.9–100.0%) against ESBL-, pAmpC-, MBL- and OXA-48-like-producing *Escherichia coli.* SPR741 also increased significantly the mecillinam coverage against ESBL-, MBL- and OXA-48-like-producing *K. pneumoniae* (to 80.0–96.0% from 0.0–49.5% susceptible). Temocillin-SPR741 susceptibility rates increased to 97.8–100.0% from 65.2–88.7% when applying the systemic breakpoint against ESBL-, pAmpC-, and KPC-producing *E. coli.* Temocillin-SPR741 inhibited all KPC-producing *E. coli* and 94.6% of KPC-producing *K. pneumoniae* when applying the urinary breakpoint (≤32 mg/L). When combined with SPR741, ceftazidime and piperacillin-tazobactam were very active (93.8–100.0%) against pAmpC-, ESBL-, and OXA-48-like-producing *E. coli*, while the susceptibility rate of piperacillin-tazobactam-SPR741 increased to 98.0% from 65.3% when tested alone against ESBL-producing *K. pneumoniae* (using CLSI breakpoints). Other combinations using cefoxitin, meropenem, aztreonam, cefotaxime and cefepime were less active against this challenge set of organisms.

Conclusions: These *in vitro* data indicate that SPR741 significantly potentiates the antimicrobial activity of mecillinam, temocillin, ceftazidime and piperacillin-tazobactam against a challenge set of pathogens. These data support the use of SPR741 in combination with several SOC agents.