Bactericidal Activity of Ceftazidime in Combination with SPR741 Against Susceptible, Extended-Spectrum Beta-Lactamase Producing, and Multidrug Resistant *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* Species

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**ABSTRACT**

Background: SPR741 is a novel polymyxin B derivative with minimal intrinsic antibacterial activity and reduced nephrotoxicity. SPR741 interacts with the outer membranes of gram-negative (G−) bacteria enhancing permeation of co-administered compounds such as ceftazidime (CAZ).

Materials and methods: The antibacterial activity of CAZ alone and with mg/ml SPR741 was assessed against clinically relevant susceptible, multidrug-resistant and CAZ-resistant isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter* species using the CLSI broth microdilution (MIC) methods. Selected CAZ-resistant susceptible and resistant isolates of *E. coli* and a colistin-resistant isolate of K. pneumoniae were also assessed using a CLSI time-kill method.

Results: SPR741 at 8 mg/ml reduced MICs of CAZ against 35% E. coli strains by 4-8 fold. 50% by 2 fold and reduced MICs of CAZ against 16.5% K. pneumoniae strains by 4 fold. 16.5% by 2 fold. SPR741 showed MICs of 1/16 of CAZ resistant *E. coli* and 8 mg/ml CAZ resistant *K. pneumoniae* isolates into the susceptible range using the CLSI time-kill method. CAZ in combination with SPR741 at 8 mg/ml was bactericidal at the MIC against 35% tested *E. coli*, K. pneumoniae, and *Enterobacter* isolates. CAZ in combination with SPR741 demonstrated a 3-log10 CFU/ml reduction of CAZ susceptible *E. coli* ATCC 25922 viability at 24 h within four hours. CAZ + SPR741 showed a similar rapid bactericidal effect against CAZ resistant clinical isolates (E. coli, *K. pneumoniae* and K. pneumoniae *K244/04) of 4 and 2x MIC within four hours, respectively, similar to CAZ alone but at a significantly lower concentration of CAZ.

Conclusions: These data illustrate that SPR741 significantly enhances the antimicrobial activity and viability of CAZ against clinical isolates of Enterobacteriaceae. These data support the use of SPR741 in combination with this SOC agent.

**INTRODUCTION**

Resistance to Gram-negative bacteria is a growing threat and has impacted the utility of SOC agents, especially in high-risk populations. SPR741 is a novel cationic polymyxin B derivative with minimal intrinsic antibacterial activity and reduced nephrotoxicity. SPR741 interacts with the outer membrane of Gram-negative (G−) bacteria, compromising the integrity of the lipopolysaccharide (LPS) barrier, thus enhancing penetration and activity of antimicrobial compounds such as ceftazidime (CAZ) when co-administered.

**METHODS**

- The potency and bactericidal activity of CAZ alone and in combination with SPR741 (at 8 mg/ml) was assessed in vitro vs. 30 clinically relevant susceptible, multidrug-resistant (MDR) and CAZ-resistant isolates of *E. coli*, *K. pneumoniae*, and *Enterobacter* species using CLSI methods M7-A10 and M49-A2 to determine both minimum inhibitory concentrations (MIC) and CLSI method M90-A2 to determine minimal bactericidal concentrations (MBC).
- MIC susceptible and resistant isolates of *E. coli* and a CAZ resistant isolate of *K. pneumoniae* were also assessed using CLSI time-kill method M26-A. In brief, cultures were grown to log phase in CAMHB, diluted to ≤2.0CFU/μl, in 18ml CAMHB containing antimicrobials of 3x-32x MIC and incubated at 35° ± 0.2°C. Viability was determined by plating for CFU/ml on agar.
- CAZ + SPR741 demonstrated a 3-log10 CFU/ml reduction of CAZ susceptible *E. coli* ATCC 25922 viability at 2x MIC within four hours.
- CAZ + SPR741 showed a similar rapid bactericidal effect against CAZ resistant clinical isolates (E. coli *K. pneumoniae* and *K. pneumoniae* *K244/04*) at 4x and 2x MIC within four hours, respectively, similar to CAZ alone but at a significantly lower concentration of CAZ.

**RESULTS**

**CONCLUSIONS**

These data demonstrate that SPR741 enhances the potency of CAZ and the combination exhibits robust bactericidal activity against clinically relevant species of Enterobacteriaceae, and thus represents a promising treatment option for infections caused by CAZ susceptible and non-susceptible bacterial isolates.

**REFERENCES**

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