S-649266, a Novel Siderophore Cephalosporin: In Vitro Combination Effect of S-649266 and Other Antibiotics against Gram-negative Bacteria

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ABSTRACT

Background: The prevalence of carbapenem-resistant and multidrug-resistant (MDR) Gram-negative bacteria has become a serious healthcare problem all over the world. However, currently available therapeutic options for infections caused by MDR Gram-negative bacteria are limited, which is a major obstacle to the effective treatment of serious infections caused by Gram-negative bacteria such as Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae. MDR Gram-negative bacteria are currently treated with combination therapy. Combination Therapy is usually used for the treatment of the MDR Gram-negative bacteria. It is an important factor to investigate the synergistic actions between agents for the combination for the constitution of effective therapy in this study. A new combination activity of S-649466 with other antibiotics was evaluated against Gram-negative bacteria.

Materials/methods: Combination effects of S-649466 and other antibiotics were evaluated by checkerboard methods and time-killing studies using non-optimised medium, which was made with Chinese cheese. A total of 32 monopotent (MMP) non-susceptible strains, which were isolated from the in vitro study conducted in 2012, were tested. These 32 strains were classified into 4 groups: Pseudomonas aeruginosa, Acinetobacter baumannii, Enterobacteriaceae, and Klebsiella pneumoniae. The antimicrobial agents, and 20 antibacterial agents and also included 3 KEK-producing strains, tested antibiotic for the combination were Metfam, Ampicillin, and Amikacin (A). In checkerboard studies, the lowest MIC was used to determine the combination effect which was categorized into three groups: synergistic, indifferent, and antagonistic. In separate time-kill studies, combination effects of each two MIC concentrations of S-649466 with Metfam, Aminoglycoside, and CEK producing agents, were tested to determine the bactericidal effect of S-649466 combined with each antibiotic. 

RESULTS: The combination of S-649466 and MMPH showed the synergistic effect against 25.8% of Pseudomonas aeruginosa and 62.9% of A. baumannii, and 11.9% of P. aeruginosa. None of the combinations of S-649466 and the reference agents (Metfam, Aminoglycoside) showed antagonism. Aggregated to all tested strains in the time-kill studies, synergistic effects were observed for combination of S-649466 and Metfam or Metfam and AMP from the results that the combination use more than 3 mg/l, decreased in number of viable cells at 24 hours compared with the single treatment of each antibiotic. However, significant synergistic effects between S-649466 and Amp were observed for S of 9 strains.

Conclusions: The combination of the S-649466 and other antibiotics showed synergistic effect and did not show antagonism, suggesting the potential use of S-649466 combined with other agents for the treatment of MDR Gram-negative bacteria infections. The combination of S-649466 and Metfam demonstrated a greater likelihood of synergy, compared with the combination with AMP or CEK.

REFERENCES