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Paper Poster Session I

New antibacterial drugs

S-649266, a novel siderophore cephalosporin: binding affinity to PBP and *in vitro* bactericidal activity

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Objectives:
S-649266 is a novel catechol-substituted siderophore cephalosporin antibiotic with potent antibacterial activity against Gram-negative bacteria including multidrug-resistant strains. This study investigated binding affinity of S-649266 to penicillin binding proteins (PBPs) of *Escherichia coli* and *Pseudomonas aeruginosa*, and *in vitro* bactericidal activity of S-649266 against *E. coli, Klebsiella pneumoniae*, *P. aeruginosa*, and *Acinetobacter baumannii*.
Methods:
E. coli NIHJ JC-2 and *P. aeruginosa* ATCC 27853 were used for investigation of binding affinity to PBPs. The membrane fraction was incubated with benzylpenicillin [benzyl-^{14}C] potassium in the presence of various concentrations of the substrates. The incubated membrane fraction was applied to SDS-PAGE, and the radioactivity was determined to evaluate the binding affinity of the substrates to each PBP. The binding affinity of S-649266 was compared with that of ceftazidime. The *in vitro* bactericidal activities were evaluated against a strain of *E. coli*, 3 strains of *K. pneumoniae* including KPC-2 producer and NDM-1 producer, 2 strains of *P. aeruginosa* including IMP-1 producer, and 2 strains of *A. baumannii* including multidrug-resistant strains. Cation adjusted Mueller Hinton broth supplemented with or without apo-transferrin was used except for the experiment of *A. baumannii* where Iso-Sensitest broth supplemented with or without apo-transferrin was used. Apo-transferrin was added to create the iron deficient conditions. The *in vitro* bactericidal activities were compared with those of ceftazidime.
Results:
IC_{50}s of S-649266 with PBP3 of *E. coli* JC-2 and *P. aeruginosa* ATCC 27853 were 0.04 mg/L and 0.06 mg/L, respectively. On the other hand, IC_{50}s of S-649266 with other PBPs were more than 10 times higher than those with PBP3. IC_{50}s of ceftazidime with PBP3 of *E. coli* JC-2 and *P. aeruginosa* ATCC 27853 were 0.45 and 0.09 mg/L respectively. As well with S-649266, IC_{50}s of ceftazidime with other PBPs were more than 10 times higher than those with PBP3. S-649266 achieved 1-$\log_{10}$ reduction at 4 x MIC against all the tested strains, and showed 2- to 3-$\log_{10}$ reduction with higher concentrations against all the teste strains of *E. coli*, *K. pneumoniae* including KPC-2 producing strain and NDM-1 producing strain, *P. aeruginosa* including IMP-1 producing strain, and *A. baumannii* including multidrug-resistant (MDR) strain.
Conclusion:
S-649266 showed high binding affinity with PBP3 of *E. coli* JC-2 and *P. aeruginosa* ATCC 27853, which indicated that S-649266 showed antibacterial activities by inhibiting PBP3 of Gram-negative bacteria. S-649266 killed all the tested strains at 4 x MIC, and showed better bactericidal activities with higher concentrations against all the tested strains including MDR pathogens. These results showed the potential of S-649266 for the treatment of the infection caused by MDR pathogens, which will meet unmet medical needs.