**ABSTRACT**

**Background.** *S.649266*, which was discovered by Shionogi & Co., Ltd., is a novel cefathiamid-substituted cephalosporin with potent activity against Gram-negative pathogens including multidrug-resistant (MDR) isolates. In this study, to elucidate therapeutic efficacy of *S.649266* was evaluated in rat lung infection models.

**Methods.** Exposure profile of free concentrations of *266* in human plasma was determined in cannulated rats derived from the PK profile with 2 g dose by 1 h infusion in healthy volunteers (phase 1). The 2 g human PK profiles were modeled for both 1 and 3 h infusion. With the recombinant human PK profiles, the efficacy of *S.649266* was evaluated against 2 strains of *NDM-1* producing *K. pneumoniae* and 3 strains of *KPC-producing K. pneumoniae* in rat lung infection model.

**Results.** The 1 h infusion of *S.649266* showed efficacies against all the strains except *K. pneumoniae K22*, but the treatment with 3 h infusion of *S.649266* decreased viable cells to below the limit of detection. Viable cell numbers in lungs were as follows:

**INTRODUCTION**

*S.649266* is a new para-oxymethylene cephalosporin antibiotic with antibacterial activity against Gram-negative bacteria. *S.649266* has unique structural features including a para-oxymethylene substituent that efficiently inactivates penicillin-binding proteins and utilizes the bacterial inner membrane transport system to permeate the outer membrane of Gram-negative pathogens and is stable to hydrolysis across a wide range of plasmidase-producing strains and enteric enteric enzymes. These studies were undertaken to evaluate the efficacy of the *S.649266* profile from a 2 g dose administered as a 1 h intravenous infusion to healthy volunteers and as a 2 g dose administered as a 3 h intravenous infusion using a computerized system to recreate the free exposure profile in cannulated rats. The recomposed exposure profile of 1 and 3 h infusion were evaluated for efficacy in a lung infection model against 3 strains of *KPC* and 3 strains of *NDM-1* producing *K. pneumoniae*.

**MATERIALS AND METHODS.**

**Animals.** Pathogen free (SPF) male Sprague-Dawley rat 6-8 weeks old were used throughout. Animals were housed in a ventilated isolator. Each group consisted of 5 animals for exposure studies and 3 animals for efficacy studies.

**Evaluation.** The PK profile was measured by HPLC method according to the Clinical and Laboratory Standards Institute. The MIC was determined by Etest method. The minimum effective concentration (MEC) was determined by Etest method. The MIC was determined for the bactericidal inactivation of all strains and the minimum inhibitory concentration (MIC) was determined for the bactericidal inactivation of all strains. The MEC concentration was determined for the bactericidal inactivation of all strains. The MIC concentration was determined for the bactericidal inactivation of all strains. The MEC concentration was determined for the bactericidal inactivation of all strains. The MIC concentration was determined for the bactericidal inactivation of all strains.

**RESULTS.** The 1 h infusion of *S.649266* showed efficacies against all the strains except *K. pneumoniae K22*, but the treatment with 3 h infusion of *S.649266* decreased viable cells to below the limit of detection. Viable cell numbers in lungs were as follows:

**CONCLUSIONS.** The human PK profile of *S.649266* was successfully recreated in rat. The 3 h infusion of *S.649266* showed potent efficacy against *K. pneumoniae producing NDM-1* or *KPC* causing pneumonia. The results suggest that *S.649266* is a promising antimicrobial treatment for infection strains such as *NDM-1* and *KPC* producer, and that a prolonged infusion would enhance the in vivo antibacterial activity.

**REFERENCES.**