Cefiderocol (S-649266), a novel Siderophore Cephalosporin: Pharmacodynamic Assessment by using MIC in Iron-depleted Cation-adjusted Mueller Hinton Broth (CAMHB)

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ABSTRACT (Revised)

Cefiderocol (S-649266), a novel siderophore cephalosporin, is active against Gram-negative bacilli including carbapenem-resistant strains. Effective in vitro and in vivo bacterial killing is observed in a wide variety of bacteria, including carbapenem-resistant strains (1). Cefiderocol has been shown to have potent activity against A. baumannii in a murine thigh infection model. Intravenous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model using 3 strains of A. baumannii, the inoculum was prepared with 5% MHB broth. Cefiderocol (S-649266) was used at 0.25×MIC and 0.5×MIC (Table 1). For all isolates tested, the efficacy of cefiderocol correlated well with MIC determined using ID-CAMHB which is a test medium for cefiderocol. ICR mice (male, five weeks old, neutropenic, n=5) were infected subcutaneously with 10^7 CFU of A. baumannii per mouse. Subcutaneous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model, the growth was significantly reduced (i.e. a button T>MIC). Protein binding ratios of cefiderocol in mice is 30.8%.

MATERIALS AND METHODS

Test organisms

Twelve clinical isolates of Gram-negative bacteria including carbapenem-resistant strains used were used to establish thigh/intraperitoneal infection models for the in vivo efficacy. Inoculation of 10^7 CFU of test bacteria in 5% MHB was injected subcutaneously into the leg muscle of mice. For the evaluation of cefiderocol, a three-day treatment was initiated at 2 h post infection. A. baumannii was used for the thigh infection model. For all isolates tested, the efficacy of cefiderocol correlated well with MIC determined using ID-CAMHB which is a test medium for cefiderocol. The tissue concentrations of cefiderocol were determined by high-performance liquid chromatography (HPLC).

CONCLUSIONS

Cefiderocol possesses a novel mechanisms of action different from those of structurally related drugs. Cefiderocol is a novel siderophore cephalosporin with potent activity against A. baumannii. Cefiderocol is active against Gram-negative bacilli including carbapenem-resistant strains. Effective in vitro and in vivo bacterial killing is observed in a wide variety of bacteria, including carbapenem-resistant strains. Cefiderocol has been shown to have potent activity against A. baumannii in a murine thigh infection model. Intravenous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model using 3 strains of A. baumannii, the inoculum was prepared with 5% MHB broth. Cefiderocol (S-649266) was used at 0.25×MIC and 0.5×MIC (Table 1). For all isolates tested, the efficacy of cefiderocol correlated well with MIC determined using ID-CAMHB which is a test medium for cefiderocol. ICR mice (male, five weeks old, neutropenic, n=5) were infected subcutaneously with 10^7 CFU of A. baumannii per mouse. Subcutaneous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model, the growth was significantly reduced (i.e. a button T>MIC). Protein binding ratios of cefiderocol in mice is 30.8%.

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Cefiderocol (S-649266), a novel siderophore cephalosporin, is active against Gram-negative bacteria including carbapenem-resistant strains (2). To obtain the in vitro activities which were determined using broth microdilution and cefiderocol was used at 0.25×MIC and 0.5×MIC (Table 1). For all isolates tested, the efficacy of cefiderocol correlated well with MIC determined using ID-CAMHB which is a test medium for cefiderocol. Cefiderocol was shown to have potent activity against A. baumannii in a murine thigh infection model. Intravenous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model, the growth was significantly reduced (i.e. a button T>MIC). Protein binding ratios of cefiderocol in mice is 30.8%.

Pharmacokinetic/Pharmacodynamic analysis

To examine the antimicrobial activity of cefiderocol, the efficacy of cefiderocol was investigated using the PK/PD parameters required for efficacy was evaluated for each 3 of strains. For all isolates tested, the efficacy of cefiderocol correlated well with MIC determined using ID-CAMHB which is a test medium for cefiderocol. ICR mice (male, five weeks old, neutropenic, n=5) were infected subcutaneously with 10^7 CFU of A. baumannii per mouse. Subcutaneous administration of antibiotics was initiated at 2 h post infection. For the murine thigh infection model, the growth was significantly reduced (i.e. a button T>MIC). Protein binding ratios of cefiderocol in mice is 30.8%.