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Paper Poster Session
New antibiotics against Gram-negative bacteria

Dose adjustment of S-649266, a siderophore cephalosporin, for patients requiring Haemodialysis

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Background: S-649266 is a novel parenteral siderophore cephalosporin discovered by Shionogi & Co., Ltd. which exhibits potent efficacy against various gram-negative bacteria including carbapenem resistant strains. S-649266 is mainly renally excreted and significantly dialyzable. The aim of this study is to recommend adjustment of S-649266 dose regimens for patients requiring hemodialysis (HD) based on the results in a renal impairment study and a modeling and simulation (M&S) approach.

Material/methods: The previously reported population pharmacokinetic model established the relationship of renal function (eGFR calculated by MDRD equation) to total clearance of S-649266 [Katsube T et al. ECCMID2015. P0254] was modified to incorporate clearance with HD (CL_{HD}) for describing S-649266 removal during HD. CL_{HD} of 3- to 4-hour HD was estimated from S-649266 concentrations in plasma and dialysate for 8 patients requiring intermittent HD in a renal impairment study [Echols R et al. ECCMID2015. EV0057]. The dose regimen for patients requiring HD was selected to provide daily AUC comparable to subjects with normal renal function (2 g every 8 hours [q8hr] with 3-hr infusion). Monte-Carlo simulation was employed to calculate probabilities of target attainment (PTA) for time for which free drug concentration in plasma exceeds MIC ($T_{f>MIC}$) for 75% of a dosing interval (1-$\log_{10}$ reduction in animal models) against an MIC range of 0.25 to 16 mg/L.

Results: The developed model well described the plasma S-649266 concentrations with or without the HD and the excretion of S-649266 into the dialysate on the HD session. With 3 to 4 hours of HD, 56% of S-649266 dose was removed in the dialysate. The dose regimen of 0.75 g every 12 hours (q12hr) with 3-hr infusion was selected to provide comparable AUC at the dose regimen for subjects with normal renal function. The selected dose regimen provided > 90% of PTA for a MIC of 8 mg/L on non-dialysis day. A supplemental dose of 0.75 g with 3-hr infusion immediately after the HD session was proposed, and thereby the dose regimen provided > 90% of PTA for a MIC of 16 mg/L even on the dialysis day.

Conclusions: Based on the M&S approach, the proposed dose regimen for patients requiring intermittent HD, 0.75 g q12hr with 3-hr infusion plus supplemental dose of 0.75 g just after HD provide exposure similar to that in patients with normal renal function receiving 2 g q8hr. The M&S also suggested that the proposed dose regimen would ensure > 90% PTA for 75% $T_{f>MIC}$ against the target pathogens (ie, carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacteriaceae*; MIC_{90}: 4, 2 and 16 mg/L using iron-deficient medium). Dose regimens for patients with continuous renal replacement therapy will be provided.