EP0135
ePoster Session
Update on colistin PK/PD

Subacute toxicity and pharmacokinetics of colistin in rats following two intravenous doses of colistin sulfate and dextrin-colistin conjugates

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Background: The recent emergence of plasmid-mediated polymyxin resistance highlights the urgent need for new antibiotic compounds or reformulation of promising antibiotic drugs that are currently restricted due to high toxicity or poor pharmacokinetics. We have developed dextrin-colistin conjugates, which demonstrated comparable antibacterial activity to Colomycin®, but with reduced *in vivo* toxicity and prolonged plasma half-life. The objective of this Study was to compare the pharmacokinetics and toxicity of 8-hourly intravenous doses of colistin sulphate and dextrin-colistin conjugate in rats.

Material/methods: Dextrin-colistin conjugates were synthesised using 1.1 mol% succinoylated 8,000 g/mol dextrin with a colistin content of 6.9% w/w. Colistin sulfate (Sigma Aldrich, USA; 20 mg/kg) or dextrin-colistin conjugate (0.5, 5, 20 mg/kg colitin equiv.) were dissolved in 0.9% w/v sterile saline, filtered (0.22 μm) and administered intravenously to 3 Sprague-Dawley rats with a sham intrabronchial respiratory tract infection (agar plug). One hour post-infection, each treatment group were administered two doses intravenously, 8 hours apart. Blood samples were collected 5 min after each dose and 12 and 16 h after the first dose. Plasma concentrations of colistin were quantified by Bioo MaxSignal® ELISA (Bioo Scientific Corporation, USA). Cage-side observations of general well-being and behaviour were made throughout the study.

Results: Repeat doses of dextrin-colistin conjugate were well tolerated at all dose levels, however animals administered colistin sulfate at 20 mg/kg appeared agitated then lethargic after the first dose and one animal died 10 min after the second dose. Analysis of plasma colistin concentration showed higher levels and extended retention of colistin in rats treated with an equivalent dose of dextrin-colistin conjugate compared to colistin sulfate. Antibiotic resistance often occurs when bacteria are exposed to suboptimal concentrations of antibiotic, therefore it is encouraging that dextrin-colistin conjugates were better tolerated at higher concentrations in this study. Accumulation of conjugates at sites of infection is also expected to increase their efficacy and reduce the emergence of resistance.

Conclusions: This study demonstrates the safety of repeat dosing with dextrin-colistin conjugates, and defines safe dosing levels for subsequent *in vivo* efficacy models of infection.