EV0208

ePoster Viewing

Antimicrobials: new antimicrobials

Efficacy of novel extended spectrum pleuromutilins against *E. coli in vitro* and *in vivo*

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Objective

Among the resistant bacterial pathogens causing serious infections *E. coli* is one of most worrisome since multi-drug resistant strains continue to emerge in both the nosocomial and the community setting leaving no viable treatment options.
The Extended Spectrum Pleuromutilins (ESP) are a new generation of pleuromutilin antibiotics with efficacy against important Gram-negative pathogens, including multi-resistant Enterobacteriaceae. ESP cover a majority of bacterial pathogens imposing urgent and serious threats according to CDC. Those include multi-drug resistant *E. coli*, *S. aureus*, *K. pneumoniae*, and *S. pneumoniae*, among others. This study investigated the *in vitro* and *in vivo* efficacy of four new ESP derivatives (BC-7634, BC-9074, BC-9529 and BC-9563) against *E. coli* in comparison to current treatment options and evaluated the metabolic stability and cytotoxicity in human hepatocytes.

Methods

The ESP were evaluated for their *in vitro* activity against *E. coli* (*n* = 32) including 78.1 % ESBL (TEM, CTX-M) producing strains by broth microdilution according to CLSI (M7/A9). For evaluation of the metabolic stability and cytotoxicity primary human hepatocytes were used.

The therapeutic potency of ESP *in vivo* was evaluated in a lethal murine sepsis model. Mice were infected intraperitoneally with an inoculum of ~10^6 CFU *E. coli* per mouse. Simultaneously, animals were treated with incrementing doses of the test compounds. Survival was recorded for 96 h. The total daily dose required for survival of 50 % of mice at 96 h post infection (ED_{50}) and 95 % confidence limits were determined by binary probit analysis.

Results

All four ESP exhibited potent antibacterial activity against *E. coli* being comparable to that of tigecycline. The MICs ranged from 0.06–2 µg/mL, with all isolates being inhibited at concentrations of ≤ 2 µg/mL. The activity was completely unaffected by the production of ß-lactamases which included TEM-, SHV-, CTX-M- and KPC- type ESBLs or metallo-ß-lactamases (NDM-1).

Testing in primary human hepatocytes confirmed the metabolic stability and low cytotoxic potential of these new derivatives.

In the murine bacteremia model all selected ESP showed good efficacy with the most active ESP being comparable to tigecycline (ED_{50} of 0.45 mg/kg/day). BC-7634, BC-9074, BC-9529, and BC-9563 displayed ED_{50} values of 3.46 mg/kg/day, 0.78 mg/kg/day, 3.75 mg/kg/day and 2.30 mg/kg/day, respectively, correlating well with $MIC_{50/90}$: 2/4 µg/mL, 0.12/0.5 µg/mL 0.5/1 µg/mL and 0.5/1 µg/mL.

Conclusion

The potent *in vitro* activity of ESP against *E. coli* including highly resistant isolates could be translated into good *in vivo* efficacy. Mice with bacteremia caused by *E. coli* were successfully treated by ESP with ED_{50} values being comparable to that of tigecycline. The potent efficacy, high metabolic stability and low potential for cytotoxicity warrant the further development of ESP for the treatment of serious infections caused by *E. coli*.