**ABSTRACT**

Background: The emergence and spread of multidrug-resistant (MDR) Enterobacteriaceae is limiting available options to treat infections caused by these pathogens. SPR206 is a polymyxin analogue that exhibits potent in vitro activity against key Gram-negative pathogens like Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli (Ec) and Klebsiella pneumoniae, including MDR variants. Here, we describe the efficacy of SPR206 in an immunocompetent murine ascending urinary tract infection (UTI) model using Ec ATCC700928 and Ec UTI89 (Ec89) as infecting organisms.

Material/methods: The minimum inhibitory concentration (MIC) against Ec700928 and Ec89 were determined for SPR206 and polymyxin B (PMB) using CLSI methodology. Female C3H/HeN mice were maintained on 5% glucose drinking water for 5 days prior to infection. Mice were infected by inoculating the bladder with 10^5 CFU/mL of Ec ATCC700928 (Ec700928) or Ec UTI89 (Ec89) in PBS, respectively. Treatment started 1-day post infection and mice were euthanized 4 days after the first treatment. Kidney tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

Results: The MIC of PMB and SPR206 for Ec700928 was determined to be 0.125 and 0.03 mg/L, respectively. The MIC for Ec89 was 0.06 mg/mL and 0.125 mg/L, respectively. In both studies, robust growth of the infecting organism in kidney tissue of 1.0 log10 CFU/g between day 1 and day 4 was observed. Administration of PMB and SPR206 at 4 mg/kg q8h SC for 3 days reduced the burden of Ec89 by 2.9 and 3.0 log CFU/g compared to the day 1 control. Administration of PMB and SPR206 at 4 mg/kg q8h SC for 3 days reduced the burden of Ec700928 by 1.5 and 4.1 log CFU/g compared to the day 1 control, respectively.

Conclusions: The in vivo pharmacology studies described herein demonstrate that SPR206 exhibits similar, or superior, efficacy to PMB in immunocompetent murine ascending UTI infections. These data support the continued development of SPR206 for intravenous administration in the hospital setting for the treatment of serious Gram-negative infections.

**METHODS**

- The minimum inhibitory concentration (MIC) against Ec700928 and Ec89 were determined for SPR206 and polymyxin B (PMB) using CLSI methodology.
- The infection was established similar to that described in Hung et al.
- Female C3H/HeN mice were maintained on 5% glucose drinking water for 5 days prior to infection.
- Mice were infected by inoculating the bladder intrareurally (UTI) via catheter.
- SPR206 and PMB were dosed at various concentrations by scutaneous (SC) administration, every 8 hours (q8h) for 3 days.
- Treatment started 1 day post-infection and mice were euthanized 4 days after the first treatment. Kidney tissues were homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

**RESULTS**

Table 1. MIC of strains used in the studies

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMB</td>
<td>0.125</td>
</tr>
<tr>
<td>SPR206 0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>LEVO</td>
<td>0.06</td>
</tr>
<tr>
<td>E. coli ATCC700928</td>
<td>0.125</td>
</tr>
<tr>
<td>E. coli UTI89</td>
<td>0.06</td>
</tr>
</tbody>
</table>

![Figure 1. Structure of SPR206](image)

![Figure 2. Burden reduction in Ec ATCC90028 with PMB or SPR206 administration](image)

![Figure 3. Burden reduction in Ec UTI89 with PMB or SPR206 administration](image)

**REFERENCES**

1. CLSI M07-A10: Methods for Dilution Antimicrobial Susceptibility Testing for Aerobic Bacteria

**ACKNOWLEDGMENTS**

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