A Pharmacokinetic-Pharmacodynamic Evaluation of the Novel Antibiotic Potentiatior, SPR741, In Combination With Piperacillin/Tazobactam Against Enterobacteriaceae

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INTRODUCTION
Antimicrobial resistance has become one of the largest threats to global health.

SP-9A, a novel polymyxin B derivative with minimal innate antibacterial activity and reduced non-clinical nephrotoxicity, acts as a potentator when administered in combination with antibiotics against Gram-negative pathogens.

Hence, we describe a series of 24- and 48-hour one-compartment in vitro studies designed to activate a series of antibiotics in a manner that mimics administration in combination with antibiotics against Gram-negative pathogens.

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METHODS

Ampicillin and Ceftriaxone Isolates

Ampicillin (ampicillin) and Ceftriaxone (ceftriaxone) are antibiotics used in combination to treat infections caused by Gram-negative bacteria. These antibiotics are often used in clinical settings as a synergistic therapy to overcome bacterial resistance.

Beta-Lactamases

Beta-lactamases are enzymes produced by bacteria that can inactivate beta-lactam antibiotics, leading to treatment failures. Ampicillin, for instance, can be inactivated by these enzymes, making it ineffective against certain bacterial strains.

Susceptibility Testing

Susceptibility testing is a method used to determine the sensitivity of a bacterial isolate to different antibiotics. This involves exposing the bacteria to varying concentrations of antibiotics and measuring the growth inhibition.

RESULTS

Pharmacokinetic-Pharmacodynamic Analysis

Data from the dose-ranging studies were pooled and evaluated using PK/PD models and non-linear least squares regression.

The relationship between change in log CFU/ml from baseline at 24 hours and the free-drug ratio of the area under the concentration-time curve to the MIC (AUC/MIC) was determined for the SPR741/AUC/MIC value of each challenge isolate as described in the susceptibility study, and was evaluated.

Once the pharmacokinetic-pharmacodynamic (PK/PD) relationship that best described the activity of SPR741 in combination with PIP/TAZ was identified, the SPR741 free-drug AUC/MIC values determined with non-linear least squares regression and logistic regression are shown.

Table 1: Known resistance mechanisms and susceptibility results of the challenge isolates evaluated in this one-compartment in vitro infection model.

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Minimum Inhibitory Concentration (MIC)</th>
<th>MIC Value (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa</td>
<td>&gt;2</td>
<td>0.1</td>
</tr>
<tr>
<td>E. coli</td>
<td>&gt;2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

CONCLUSIONS
The use of dose-ranging and susceptibility studies conducted using the one-compartment in vitro models demonstrated that SPR741 enhanced the effectiveness of PIP/TAZ against drug-resistant isolates.

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REFERENCES


Figure No. 1: CARB-X 8R4

Figure No. 2: ICPD 8R4