In Vitro Activity of Omadacycline (PTK796) in Broth, Broth plus Lung Surfactant or Human Serum

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ABSTRACT

Background
Determine the effects of lung surfactant and human serum on the in vitro activity of omadacycline (OMC).

Methods
MICs were performed in three systems. Cation-adjusted Mueller Hinton broth was used according to standard CLSI microdilution procedures, in addition to broth enriched with 1% bovine serum, and 25%-50% human serum. The strains included were clinical Gram-positive (S. aureus, S. pneumoniae), as well as Gram-negative (E. coli and H. influenzae), selected to include a range of susceptibility and appropriate ATCC controls. Doxycycline (DOXY) and daptomycin (DAPT0) were tested as comparators.

Results
MIC ranges in all three systems are shown below (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Organism</th>
<th>N</th>
<th>Condition</th>
<th>Range MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus 6</td>
<td>Broth</td>
<td>0.125-0.5</td>
<td>0.10-4</td>
</tr>
<tr>
<td>S. pneumoniae 5</td>
<td>Broth</td>
<td>0.03-0.06</td>
<td>0.03-4</td>
</tr>
<tr>
<td>S. pneumoniae 3</td>
<td>Broth</td>
<td>0.03-0.06</td>
<td>0.03-0.4</td>
</tr>
<tr>
<td>S. pneumoniae 3</td>
<td>Serum (50%)</td>
<td>0.03</td>
<td>0.125-0.5</td>
</tr>
<tr>
<td>E. coli 6</td>
<td>Broth</td>
<td>0.5-4</td>
<td>0.5-32</td>
</tr>
<tr>
<td>E. coli 6</td>
<td>Serum (50%)</td>
<td>0.5</td>
<td>0.5-3.2</td>
</tr>
<tr>
<td>H. influenzae 6</td>
<td>Broth</td>
<td>0.5-4</td>
<td>0.5-32</td>
</tr>
<tr>
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<td>Serum (50%)</td>
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Conclusions
MICs of omadacycline did not increase with the addition of surfactant or serum for either Gram-positive or Gram-negative organisms. The in vitro activity of DAPT0 was markedly affected by surfactant; as well as by bovine serum, with high protein binding character. DOXY activity was not affected by surfactant, but exhibited significant decreases in activity in the presence of serum. The inhibition of activity of DAPT0 by lung surfactant has been suggested as the explanation for its lack of activity in persistent in pneumonia. (Gibbons, JL et al. JID 191(241-252): 2005). In contrast, OMC was not affected by surfactant. This finding supports the potential use of OMC in treating pneumonia caused by susceptible bacteria.

INTRODUCTION

Omadacycline (OMC, formerly PTK796) is a novel aminomethylcyclcline with a spectrum of activity consistent with its potential utility in the treatment of community-acquired pneumonia. The failure of daptomycin in pneumonia has been attributed to interactions of daptomycin with lung surfactant, compromising its ability to kill bacteria in lung tissue. It has also been shown that strong interactions with serum can adversely affect efficacy and this is also demonstrable in vitro. In order to determine the effects of lung surfactant and human serum on the in vitro activity of omadacycline, MICs were done in three systems. Cation-adjusted Mueller Hinton broth or Haemophilus test medium was used according to standard CLSI microdilution procedures, in addition to broth enriched with 1% bovine serum, and 25%-50% human or mouse serum. Appropriate quality control strains were obtained from the American type Culture Collection (ATCC, Manassas, VA). S. aureus ATCC 29213, S. pneumoniae ATCC 49619, and E. coli ATCC 25922. H. influenzae ATCC 49247.

MICROBIOLOGY METHODS

Materials
- Cation-adjusted Mueller Hinton broth (CAMHB, BBL)
- Compounds
  - Omadacycline (P000949-147, Paratek Pharmaceuticals, Inc. Boston MA)
  - Daptomycin (P000001-8, Cubist Pharmaceuticals, Lexington MA)
  - Doxycycline (P000001-8, Paratek Pharmaceuticals, Inc. Boston MA)
  - Mouse serum (Equitech BLOQ, NC)

Susceptibility testing results are shown in Tables 2-5 for S. aureus, S. pneumoniae, E. coli or H. influenzae.

- Omadacycline MICs were not affected by the addition of serum or lung surfactant to the cation-adjusted Mueller Hinton broth or Haemophilus test medium.
- Daptomycin MICs increased with the addition of serum.
- Doxycycline MICs increased in the presence of serum or lung surfactant.

RESULTS

S. aureus ATCC 29213 Broth
- 0.25 (0.125-0.25)

S. pneumoniae ATCC 49619 Broth
- 0.125 (0.062-0.125)

E. coli ATCC 25922 Broth
- 0.06 (0.03-0.125)

H. influenzae ATCC 49247 Broth
- 0.125 (0.062-0.25)

Table 2

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CONCLUSIONS

- Omadacycline (PTK796) in vitro activity was not affected by the addition of lung surfactant or serum.
- These results support the potential use of omadacycline in treating pneumonia caused by susceptible bacteria.