**In-vitro activity of the novel fluorocycline TP-6076 against carbapenem non-susceptible Acinetobacter baumannii**

Harald Seifert¹, Danuta Stefanik¹, Joyce A. Sutcliffe², Paul Higgins¹

¹Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany
²Tetraphase Pharmaceuticals, Watertown, MA, USA

**Abstract**

Background: TP-6076 is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. The purpose of this study was to evaluate the activity of TP-6076 and comparators against global, non-duplicate isolates of carbapenem-resistant Acinetobacter baumannii (CRAB).

**Materials and methods:** Clinical isolates (n=326) were collected from various body sites in patients in ten mainly European countries from 2005-2016. Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller-Hinton broth according to CLSI guidelines. The concentration ranges tested in 2-fold dilutions were: TP-6076, 0.008–16 mg/L; amikacin, 0.125–256 mg/L; colistin, 0.03–256 mg/L; doxycycline, 0.03–32 mg/L; levofloxacin, 0.03–64 mg/L; meropenem, 0.125–256 mg/L; sulbactam, 0.06–128 mg/L; tigecycline, 0.03–64 mg/L; and tobramycin, 0.06–128 mg/L. Susceptibility was determined using CLSI 2015 breakpoints. Based on rep-PCR and MLST, isolates represented 8 worldwide clonal lineages and included 255 isolates with blaOXA-23-like, 23 isolates with blaOXA-48-like, 36 isolates with blaOXA-58-like, and 10 isolates with overexpression of intrinsic blaOXA-51.

**Methods cont.**

**Methods**

**Introduction and Purpose**

- Multidrug-resistant Acinetobacter baumannii is a growing threat leaving few therapeutic options. Carbapenem-resistance in A. baumannii mediated mainly through the action of intrinsic and acquired OXA-type enzymes is an increasing cause of concern. Efflux does not significantly affect carbapenems, however it plays a role in the intrinsic resistance to fluoroquinolones, tetracyclines, aminoglycosides and macrolides.

- TP-6076 is a novel fully synthetic fluorocycline antibiotic of the tetracycline class with in vitro activity against key Gram-negative pathogens, including multidrug-resistant Enterobacteriaceae and A. baumannii. The activity of TP-6076 was compared with anti-Acinetobacter reference drugs against well-defined A. baumannii isolates.

**Bacterial isolates**

- 326 non-duplicate carbapenem-resistant A. baumannii (CRAb) isolates were collected from various body sites in patients from eight European countries and Singapore between 2005 and 2015.

- The isolates were molecularly typed with repPCR (DiversiLab) (1) and MLST (2) and characterised for carbapenem-resistance mechanisms. They represented 6 of the 8 previously described international clonal lineages and included 255 isolates with blaOXA-23-like, 23 isolates with blaOXA-48-like, 36 isolates with blaOXA-58-like, one isolate with blaVIM-2, and 10 isolates with overexpression of intrinsic blaOXA-51.

**Methods**

**MIC testing:**

- Broth microdilution (BMD) testing in cation-adjusted Mueller-Hinton broth was performed in accordance with CLSI guidelines (3).

- The antinhibitory agents and concentration ranges tested were TP-6076, 0.008–16 mg/L; amikacin, 0.125–256 mg/L; colistin, 0.03–256 mg/L; doxycycline, 0.03–32 mg/L; levofloxacin, 0.03–64 mg/L; meropenem, 0.125–256 mg/L; sulbactam, 0.06–128 mg/L; tigecycline, 0.03–64 mg/L; and tobramycin, 0.06–128 mg/L.

**Results**

**Results cont.**

- The majority of A. baumannii isolates apart from being resistant to carbapenems were also resistant to levofloxacin and aminoglycosides and had high subbactam MICs. The resistance to colistin was 13.5%.

- The TP-6076 MIC₉₀ₐ₉ values for all isolates were 0.06/0.25 mg/L. No isolate had MIC values >0.5mg/L. Comparatively, eravacycline, tigecycline, minocycline and doxycycline MIC₉₀ₐ₉ values were 0.5/1.2, 4/8, 32/64 mg/L, respectively.

**Table 1. MIC distribution, MIC₅₀ and MIC₉₀ values of the 326 carbapenem-resistant A. baumannii isolates**

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>MIC₅₀</th>
<th>MIC₉₀</th>
<th>MIC Range</th>
<th>%S</th>
<th>%I</th>
<th>%R</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP-6076</td>
<td>0.06</td>
<td>0.25</td>
<td>0.06-0.25</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>16</td>
<td>2-32</td>
<td>86</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Colistin</td>
<td>1</td>
<td>64</td>
<td>1-128</td>
<td>99</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>3</td>
<td>10</td>
<td>1-4</td>
<td>86</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Eravacycline*</td>
<td>15</td>
<td>26</td>
<td>16-165</td>
<td>43</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2</td>
<td>76</td>
<td>18-128</td>
<td>93</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>64</td>
<td>1-128</td>
<td>92</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1*</td>
<td>22</td>
<td>1-73</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minocycline</td>
<td>11</td>
<td>46</td>
<td>8-22</td>
<td>73</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subbactam</td>
<td>3</td>
<td>12</td>
<td>8-123</td>
<td>90</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>3</td>
<td>40</td>
<td>16-163</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* susceptible breakpoint values are indicated in boldface; * no CLSI breakpoint available; ≥ ≥ 64 mg/L

**References and Acknowledgements**


This work was supported by an unrestricted grant from Tetraphase Pharmaceuticals, Inc., Watertown, MA, USA.

**Conclusions**

- TP-6076 was the most potent antimicrobial against A. baumannii isolates, including those that were resistant to imipenem/meropenem, levofloxacin, subbactam, and amikacin/tobramycin, compared to other compounds.

- TP-6076 has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.