Antimicrobial Activity of Tebipenem (SPR859) against a Global Challenge Set of Enterobacteriaceae Isolates

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Introduction

- β-lactamase enzymes constitute the main mechanism of resistance against β-lactam agents in Enterobacteriaceae.
- The increasing prevalence of β-lactam resistance challenges current antimicrobial therapy.
- Enterobacteriaceae are often heterogeneous in their ability to hydrolyze penicillins, cephalosporins, and monobactams.
- K. pneumoniae is a β-lactamase-resistant enterobacterium that is resistant to most broad-spectrum β-lactam agents, except for carbapenems.
- Carbapenems are effective against E. coli, K. pneumoniae, and P. aeruginosa.
- Tebipenem, a candidate carbapenem, has shown promise for a series of nosocomial and community infections and has significantly contributed to the rapid global increase in the cephalosporin resistance rate.
- Tebipenem is a broad-spectrum antibiotic isolated in Japan in 2000 for the treatment of infection caused by multiple resistant E. coli, and recently studied against the Tebipenem-resistant K. pneumoniae isolates that developed resistance to antimicrobial agents.

Materials and Methods

Bacterial isolates
- A total of 212 Enterobacteriaceae isolates displaying susceptible phenotypes to several agents, including broad-spectrum β-lactam agents, were selected with the following species:
  - Escherichia coli (12)
  - Klebsiella pneumoniae (11)
  - Proteus spp. (10)
  - Pseudomonas aeruginosa (6)
  - Salmonella spp. (6)
  - Enterobacter cloacae (5)
  - Citrobacter freundii (5)
- A resistant subset of Enterobacteriaceae composed of the same species listed above was selected and microbiologically characterized for the presence of ESBL-producing Enterobacteriaceae encoding blactamases, plasmid-borne AmpC, and/or cephalosporinases (127).
  - E. coli (48)
  - K. pneumoniae (40)
  - Proteus spp. (32)
- Identification of bacterial isolates was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Antimicrobial susceptibility testing
- Isolates were tested for susceptibility by both microbroth following guidelines in the CLSI M07 2014 document.
  - Antibiotic discs and an automated instrument (BD Phoenix) were utilized for both CLSI and EUTC 2010 documents.
- Quality assurance was performed by concurrently testing CLSI-recommended quality control references (E. coli ATCC 25922 and 35218; Pseudomonas aeruginosa ATCC 27853).
- Breakpoint criteria for comparator agents were from the CLSI M07 2010 (18) and EUTC 2010 (16) documents.

Results

- Tebipenem (MIC, 0.03-0.06 µg/mL) showed similar MIC values when tested against wild-type and AmpC/ESBL--producing E. coli strains (MIC, 0.03-0.12 µg/mL) and K. pneumoniae isolates (MIC, 0.03-0.12 µg/mL).
- MIC values of 0.12 µg/mL were observed against AmpC/ESBL-producing K. pneumoniae isolates (MIC, 0.12-0.50 µg/mL) and P. aeruginosa (MIC, 0.12-32 µg/mL).
- All carbapenem compounds tested herein had elevated MIC values against ESBL-producing Enterobacteriaceae (MIC, 10-32 µg/mL).

Conclusions

- Overall, tebipenem was highly potent against a current challenge set of Enterobacteriaceae that caused clinical infections in patients seen/hospitalized in US and European medical centers.
- The production of ESBL and/or plasmid-borne AmpC enzymes did not adversely affect tebipenem in vitro activity against E. coli, K. pneumoniae, or Proteus spp.
- As expected, all agents tested were less active against a challenge set of Enterobacteriaceae producing carbapenemases.
- These in-vitro results obtained for tebipenem warrant further clinical development as an option for treating infections caused by common Enterobacteriaceae species producing ESBL and/or AmpC enzymes.

Acknowledgements

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References


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Table 1 Antimicrobial activity of carbapenem agents tested against β-lactamase-producing clinical isolates included in the study

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>MIC (µg/mL)</th>
<th>E. coli (12)</th>
<th>K. pneumoniae (11)</th>
<th>Proteus spp. (10)</th>
<th>Pseudomonas aeruginosa (6)</th>
<th>Salmonella spp. (6)</th>
<th>Citrobacter freundii (5)</th>
<th>Enterobacter cloacae (5)</th>
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<tbody>
<tr>
<td>Tebipenem</td>
<td>0.03-0.06</td>
<td>≤0.015</td>
<td>0.03-0.06</td>
<td>0.06</td>
<td>0.03-0.06</td>
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<td>0.03-0.06</td>
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Table 2 Antimicrobial activity of carbapenem agents tested against AmpC/ESBL-producing clinical isolates included in the study

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>MIC (µg/mL)</th>
<th>E. coli (48)</th>
<th>K. pneumoniae (40)</th>
<th>Proteus spp. (32)</th>
<th>Pseudomonas aeruginosa (27)</th>
<th>Salmonella spp. (6)</th>
<th>Citrobacter freundii (5)</th>
<th>Enterobacter cloacae (5)</th>
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<tr>
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