Efficacy of doripenem and ertapenem against KPC-2-producing and non-KPC-producing Klebsiella pneumoniae with similar MICs

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Objectives: In the clinical setting, the choice of definitive drug therapy is typically guided by the antimicrobial susceptibility profile of the infecting organism. We evaluated the activity of doripenem and ertapenem against Klebsiella pneumoniae isolates with similar MICs that exhibited KPC-based and non-KPC-based genotypes.

Methods: Five doripenem-non-susceptible K. pneumoniae isolates, three producing KPC carbapenemases and two exhibiting porin modifications plus AmpC β-lactamase production, were tested in a neutropenic murine thigh infection model. The ertapenem MIC for all isolates was 32 mg/L. Regimens of 2 g of doripenem every 8 h (4 h infusion) and 1 g of ertapenem every 24 h (0.5 h infusion) simulating human concentration–time profiles were administered 2 h after inoculation. The change in bacterial density was evaluated after 24 h of therapy.

Results: Consistent with the observed MICs, treatment with ertapenem resulted in minimal activity against all isolates tested. When comparing the activity of doripenem between the KPC and non-KPC producers with doripenem MICs of 8 mg/L, significantly better activity was noted for the non-KPC producer (P < 0.001). Likewise, when comparing the two KPC-producing isolates with doripenem MICs of 24 mg/L and >32 mg/L with the non-KPC producer with an MIC of 32 mg/L, significantly greater activity was noted for the non-KPC producer (P < 0.001).

Conclusions: When doripenem MICs were similar, activity was greater for non-KPC-producing isolates when compared with KPC producers. While the in vitro MIC is typically the sole method utilized to aid in drug selection, these data suggest that the genetic driver behind these MICs may also play a role in predicting in vivo activity.

Keywords: carbapenemases, mechanism of carbapenem resistance, genotypes, antimicrobial susceptibility profiles

Introduction

The KPC family of β-lactamas have been reported in many species of Enterobacteriaceae and threaten the utility of carbapenems. This is of great concern because carbapenems are commonly considered the treatment of choice for infections caused by multidrug-resistant Enterobacteriaceae.1-3 Importantly, while KPC production has been noted as an emerging threat to carbapenems, other enzyme- and non-enzyme-based resistance mechanisms cannot be discounted in the evolving phenotypic profiles of these organisms.4-8 In most hospitals, clinical microbiology laboratories report the MICs and subsequent antimicrobial susceptibility profile of the infecting organism. While this information is used to drive therapeutic selection, it is possible that the genotypic profile behind this MIC may play additional roles in predicting therapeutic outcomes. Previous studies conducted by our group observed minimal activity with humanized doripenem against KPC-producing Klebsiella pneumoniae, but other resistance mechanisms were not evaluated.9 In this study, we evaluated the activity of human simulated regimens of doripenem and ertapenem against MIC matched K. pneumoniae isolates exhibiting KPC-based and non-KPC-based resistance genotypes within the neutropenic murine thigh infection model.

Methods

Commercially available doripenem (Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ, USA) and ertapenem (Merck & Co., Inc., Whitehouse Station, NJ, USA) were used for in vivo studies. Immediately prior to experimentation, each drug was reconstituted and diluted with normal
Impact of KPC production on carbapenem activity

Table 1. MICs and mechanisms of carbapenem resistance in K. pneumoniae isolates

<table>
<thead>
<tr>
<th>Isolate</th>
<th>doripenem (MICs)</th>
<th>ertapenem (MICs)</th>
<th>Genotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KP430</td>
<td>8</td>
<td>&gt;32</td>
<td>porin+ACT-1</td>
<td>KPI^{11}</td>
</tr>
<tr>
<td>KP432</td>
<td>32</td>
<td>&gt;32</td>
<td>porin+ACT-1</td>
<td>KP2^{11}</td>
</tr>
<tr>
<td>KP357</td>
<td>8</td>
<td>&gt;64</td>
<td>KPC-2 producing</td>
<td>KP357^{10}</td>
</tr>
<tr>
<td>KP434</td>
<td>24</td>
<td>&gt;32</td>
<td>KPC-2 producing</td>
<td>KPS^{13}</td>
</tr>
<tr>
<td>KP431</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>KPC-2 producing</td>
<td>KP4^{13}</td>
</tr>
</tbody>
</table>

saline to achieve the desired concentration. Five previously described doripenem non-susceptible K. pneumoniae isolates, three KPC producing and two with porin modifications plus ACT-1 production, were utilized (Table 1).^{10,11} Doripenem and ertapenem MIC values were determined by Etest, according to the manufacturer’s specifications (bioMerieux North America). The study was reviewed and approved by the Hartford Hospital Institutional Animal Care and Use Committee. Animals were maintained and used in accordance with National Research Council recommendations and were provided food and water ad libitum. The well-described neutropenic mouse thigh infection model was utilized for all in vivo assessments.\(^{9}\) The humanized antimicrobial dosing regimens as determined and validated by our group simulated a non-FDA-approved, high, prolonged-infusion dose of 2 g every 8 h with a 4 h infusion for doripenem and the standard FDA-approved dose of 1 g every 24 h with 30 min infusion for ertapenem.\(^{12-14}\) To compare antimicrobial efficacy between regimens, a Student’s t-test or a Mann–Whitney U-test, as appropriate, was used. A P value ≤0.05 was defined as statistically significant.

Results

The results of the efficacy studies are shown in Figure 1. The bacterial densities of thighs from 0 h control mice ranged from 5.66 to 6.39 log\(_{10}\) cfu. Isolates grew to 7.56–9.28 log\(_{10}\) cfu after 24 h in untreated control animals. Consistent with the observed MICs, treatment with ertapenem resulted in minimal activity against all isolates tested. When comparing the activity of doripenem between the KPC and non-KPC producers with doripenem MICs of 8 mg/L, significantly better activity was noted for the non-KPC producer (−1.5 ± 0.2 versus −0.7 ± 0.2 log\(_{10}\) cfu, P < 0.001). Likewise, when comparing the two KPC-producing isolates with doripenem MICs of 24 and >32 mg/L with the non-KPC producer with an MIC of 32 mg/L, significantly greater activity was noted for the non-KPC producer (−1.5 ± 0.8 versus −0.3 ± 0.2 and 1.1 ± 0.4 log\(_{10}\) cfu, P < 0.03 and P < 0.001, respectively).

Discussion

Previous studies conducted by our group that utilized the same pharmacodynamically optimized human exposures of doripenem against Pseudomonas aeruginosa and KPC-producing K. pneumoniae in the neutropenic thigh infection model revealed that while maximal activity was achieved against P. aeruginosa with MICs ≤16 mg/L,\(^{12}\) only static effects were noted against KPC-producing K. pneumoniae over this same MIC range.\(^{9}\) In the current study, we found that although doripenem therapy resulted in considerable activity against K. pneumoniae with non-KPC-based resistance mechanisms and mirrored previous studies with P. aeruginosa,\(^{12}\) activity against KPC-producing isolates with the same or a similar MIC was minimal. It is important to note that while these clinical isolates were chosen based on their status of KPC production, other background resistance mechanisms are likely to exist\(^{4,6,8}\) but have yet to be evaluated. As such, future studies utilizing isogenic strains, as well as other non-KPC-based resistance mechanisms, would be prudent to confirm that these observations are directly attributable to the production of the KPC enzyme alone.

Given the notable differences in in vivo activity observed among carbapenem-resistant K. pneumoniae isolates with heterogeneous resistance mechanisms, these data suggest that identification of specific β-lactamase genes that are contributing to the observed MIC may play a vital role in the selection of more optimal therapies, which may lead to improved clinical outcomes.

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Transparency declarations
None to declare.

References