Variations and Trends in the Activity of Doripenem and Other Broad-Spectrum Agents Against Leading Bacterial Pathogens: Results From a European Surveillance Program (2003-2006)

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AMENDED ABSTRACT

Objectives: To summarize the results of a European-focused surveillance program comparing activity of doripenem and other agents tested against leading contemporary pathogens. Doripenem is a broad-spectrum investigational parenteral carbapenem in late-stage clinical development that displays enhanced activity against Pseudomonas aeruginosa compared with other marketed carbapenems. As we continue to evaluate doripenem, regional data assessing resistance patterns of targeted pathogens are needed.

Methods: Non-complex bacterial isolates (27,689) (bloodstream, 25.4%); respiratory tract, 21.6%; skin and skin structure, 8.3%; others, 15.6%) were collected from 24 medical centers in Europe during 2003-2006. Identifications were confirmed and all isolates were susceptibility tested using CLSI broth microdilution methods and interpretive criteria.

Results: At MIC values of 0.25 mg/L for Streptococcus pneumoniae, 0.5 mg/L for β-lactam-hypersensitive staphylococci and Haemophilus influenzae, and 4 mg/L for all other agents tested against leading contemporary pathogens, doripenem inhibited 100.0% of the tabulated pathogens recovered from all sources. Doripenem was broadly active against staphylococci, streptococci, and H. influenzae and at least 2-fold more potent against P. aeruginosa than either meropenem or imipenem. While ESBL phenotype rates varied considerably among Enterobacteriaceae and non-fermentative bacilli, doripenem displays particular strengths against European E. coli, K. pneumoniae, and Acinetobacter spp. (95.7% susceptible; oxacillin-susceptible; 4441). Increased resistance to penicillin (25.4%) among S. pneumoniae was noted; daptomycin results for most β-lactam-stable agents were lower (2004;48:3136-3140).

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 27,689 non-complex consecutive clinical isolates were submitted from 24 medical centers located in Europe as part of a 5-year (2003-2008) surveillance program. Isolates originated from patients with documented bloodstream (53.5%), respiratory (21.6%), skin and skin structure (8.3%), and other sites (15.6%). The distribution of founding species and strains is presented in Table 1.

Susceptibility Test Methods

All strains were tested by the broth microdilution method using validated commercially prepared panels (TRK Diagnostics, Oslo, 0.5 mg/L in cation-adjusted Mueller-Hinton broth (with 5% bored horse blood) for testing of streptococci and Haemophilus Influenzae. The broth microdilution method for testing β-lactam-hypersensitive staphylococci and Enterococcus species was performed in accordance with published CLSI criteria. Enterococcus faecalis with elevated MICs (≥8 mg/L) for ceftriaxone and/or cefotaxime and/or amoxicillin were considered ESBL-producing phenotypes. Quality control strains utilized included Escherichia coli ATCC 25922 and 35218; P. aeruginosa ATCC 27853; H. influenzae ATCC 49247, Staphylococcus aureus ATCC 29213, and Streptococcus pyogenes ATCC 19430. All quality control results were within CLSI-specified ranges (2007).

RESULTS

• Doripenem was broadly active against oxacillin-susceptible staphylococci (81.6% vs. oxacillin-resistant-staphylococci), (100.0% vs. 52.2%) for P. aeruginosa and other Enterobacteriaceae, and at least 2-fold more potent against P. aeruginosa than either meropenem or imipenem. For all other agents tested against leading contemporary pathogens, doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources.

Table 2. In Vitro Activity of Doripenem in Comparison to Selected Agents Against Leading Gram-Negative and Gram-Positive Bacteria

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<th>Organism (no. tested)</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>0.06</td>
<td>&gt;25</td>
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<td>K. pneumoniae</td>
<td>0.06</td>
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</tr>
<tr>
<td>P. aeruginosa</td>
<td>0.12</td>
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• At MIC values of 0.25 mg/L for S. pneumoniae, 0.5 mg/L for β-lactam-hypersensitive staphylococci and H. influenzae, and 4 mg/L for all other agents tested against leading contemporary pathogens, doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources.

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• Doripenem also was highly active against S. pneumoniae (99.0% susceptible; oxacillin-susceptible; 4441; 0.06 mg/L), and inhibited >8/76, respectively). Only polymyxin B (>99% susceptibility) among the β-lactam/stable agents was lower (2004;48:3136-3140).

• At MIC values of 0.25 mg/L for S. pneumoniae, 0.5 mg/L for β-lactam-hypersensitive staphylococci and H. influenzae, and 4 mg/L for all other agents tested against leading contemporary pathogens, doripenem inhibited 95.7% of the tabulated pathogens recovered from all sources.

• Daptomycin inhibited 100% of ESBL-confirmed strains (284 isolates tested) compared with 80.7% for meropenem and 76.0% for imipenem (2004;48:3136-3140).

• Doripenem is an investigational carbapenem in late-stage clinical trials showing a promising broad-spectrum profile, directed toward bacterial targets against European Enterobacteriaceae and non-fermentative bacilli.

Conclusions: Emerging global resistance has created a critical need for accelerated development and introduction of new antimicrobials. Doripenem inhibited 100.0% of ESBL-producing staphylococci and at least 2-fold more potent than other carbapenems. P. aeruginosa is a promising carbapenem displaying a broad spectrum against most common hospital pathogens, especially Enterobacteriaceae and non-fermentative bacilli.

SELECTED REFERENCES


ACKNOWLEDGEMENT

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