Activity of Doripenem Tested Against an International Collection of ESBL- and AmpC-Producing Enterobacteriaceae

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AMENDED ABSTRACT

Background: Emerging resistance (E) among Enterobacteriaceae to antibiotic (A) agents used in the treatment of serious infections is a major concern worldwide. ESBL and AmpC enzymes, among other resistance mechanisms, are responsible for the development of resistance to broad-spectrum agents useless. Doripenem (DOR), a new parental carbapenem recently in late-stage clinical development, displays inherent stability to most β-lactamases. This study compares the activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).

Methods: Non-duplicate bacterial isolates (16,246) were collected in >60 medical centers participating in the global DOR surveillance program (2005-2006). All isolates were susceptible tested using CLSI methods against DOR and comparator agents. ESBL production was confirmed using the CLSI disk agglutination method, whereas AmpC production (EA) was marked for stability by de-repressed expression of AmpC via co-inhibition with clavulanic acid.

Results: DOR results are in the Table

<table>
<thead>
<tr>
<th>Organism (no. tested)</th>
<th>AmpC</th>
<th>ESBL</th>
<th>AmpC+ESBL</th>
<th>Susceptible</th>
<th>Resistant</th>
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<td>K. pneumoniae (790)</td>
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In the tested collection of isolates, ESBLs were detected in 4%, 15%, and 3% of EC, KSP, and PM, respectively. Among comparator antimicrobials, amikacin provided the broadest activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).

INTRODUCTION

Dramatic increases in the prevalence of ESBL-producing (ESBL) and AmpC-producing (AmpC) bacteria have changed the face of empiric antimicrobial therapy in healthcare settings that deal with a high proportion of seriously ill patients, often with co-morbidities. Resistance to third- and fourth-generation cephalosporins, β-lactamase-inhibitor combinations, quinolones, and aminoglycosides has become commonplace in various geographic regions, requiring the utilization of new approaches to treatment. A new parenteral carbapenem in late-stage clinical development, displays inherent stability to most β-lactamases. This agent has been characterized as having broad activity against Gram-negative pathogens most similar to that of imipenem and against Gram-positive pathogens most similar to that of ceftazidime-susceptible (C,S). This agent was also the most potent agent tested, being 4 to 8-fold more active than either ceftazidime-susceptible or imipenem-susceptible Enterobacteriaceae expressing confirmed ESBL or inferred AmpC cephalosporinases.

RESULTS

Table 1. Activity of doripenem and comparator antimicrobial agents tested against all clinical isolates of Enterobacteriaceae expressing confirmed ESBL or inferred AmpC cephalosporinases.

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In the tested collection of isolates, ESBLs were detected in 6%, 13%, and 16% of ESBL- and AmpC-producing Enterobacteriaceae for resistance. Doripenem (DOR) inhibited >99% of all tested isolates of ESBL-producing Enterobacteriaceae (ENT). In addition to the carbapenems, cefepime (64.0% to 91.4%) and imipenem (77.0% to 98.0%) displayed high activity against ESBL and/or AmpC-producing ENT. Results:

- Among comparator antimicrobials, amikacin provided the broadest activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).
- In the tested collection of isolates, ESBLs were detected in 4%, 15%, and 3% of EC, KSP, and PM, respectively. Among comparator antimicrobials, amikacin provided the broadest activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).
- The present study was conducted to further evaluate the activity and potential use of DOR when tested against an international collection of EC, K. pneumoniae, and P. aeruginosa with documented ESBL and Enterobacter aerogenes (EA). Results from patients with documented bloodstream, respiratory, and urinary tract infections was at least 4-fold more potent than either imipenem-susceptible or imipenem-resistant isolates.
- ESBLs were detected in 4%, 15%, and 3% of EC, KSP, and PM, respectively. Among comparator antimicrobials, amikacin provided the broadest activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).

MATERIALS AND METHODS

Bacterial Strain Collection

A total of 16,246 non-duplicate consecutive clinical isolates were from patients with documented bloodstream, respiratory, and urinary tract infections. This subset was selected as part of a doripenem (DOR) clinical surveillance program for the years 2001 to 2005. Isolates originated from patients with documented bloodstream, respiratory, and urinary tract infections. The distribution of species and strains reported here include E. coli (5,327 isolates), Klebsiella spp. (1,835), P. mirabilis (905), Enterobacter aerogenes (423), Enterobacter cloacae (541), C. freundii (232), and S. marcescens (725).

Susceptibility Test Methods

All strains were tested by the Clinical & Laboratory Standards Institute (CLSI) broth microdilution method in validated 96-well plates (Trek Diagnostics, Cleveland, Ohio) using cation-adjusted Mueller-Hinton broth against a variety of antimicrobial agents representing the most common classes and examples of drugs used for the empiric or directed treatment of the indicated infections. Interpretation of MIC results was in accordance with CLSI criteria as published in the M100-S16 (2006) document. Enterobacteriaceae with elevated MIC values (>4 μg/mL) for β-lactamase-inhibitor combinations were considered ESBL-producing phenotypes; confirmatory testing was performed using ceftriaxone and cefotaxime alone and in combination with clavulanic acid and/or control strains inhibited included E. coli ATCC 25922 and 35218, and K. pneumoniae ATCC 700603.

CONCLUSIONS

- The dramatic increases in ESBL- and AmpC-producing enteric species are changing empiric therapy, with greater reliance upon combinations, fluoroquinolones, and aminoglycosides has become commonplace in various geographic regions, requiring the utilization of new approaches to treatment. A new parenteral carbapenem in late-stage clinical development, displays inherent stability to most β-lactamases. This agent has been characterized as having broad activity against Gram-negative pathogens most similar to that of imipenem.
- ESBLs were detected in 4%, 15%, and 3% of EC, KSP, and PM, respectively. Among comparator antimicrobials, amikacin provided the broadest activity of DOR against commonly occurring Amp-C and ESBL-producing Enterobacteriaceae (ENT).
- In the tested collection of isolates, ESBLs were detected in 6%, 13%, and 16% of ESBL- and AmpC-producing Enterobacteriaceae for resistance. Doripenem (DOR) inhibited >99% of all tested isolates of ESBL-producing Enterobacteriaceae (ENT). In addition to the carbapenems, cefepime (64.0% to 91.4%) and imipenem (77.0% to 98.0%) displayed high activity against ESBL and/or AmpC-producing ENT.

REFERENCES


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