Activity of Ceftobiprole Tested Against Contemporary European Enterobacteriaceae and Pseudomonas aeruginosa (2005-2006)

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Summary

Introduction

Emergence of resistance among commonly occurring bacterial pathogens has limited the utility of many penicillins and cephalosporins, driving increased utilization of carbapenems for Gram-negatives and vancomycin, dapsonamide, and linezolid for Gram-positives.[1, 10] Ceftobiprole, an expanded spectrum cephalosporin with potent activity against commonly occurring Gram-positive and negative bacteria (2, 4, 7), including resistant strains, is in late stage (phase 3) clinical development for the treatment of complicated skin and skin structure infections and pneumonia. The compound is stable to many commonly occurring β-lactamase and has a strong affinity for penicillin-binding proteins, including PBPs 2, 3, and 4 which mediate resistance to β-lactam in methicillin-resistant Staphylococcus aureus (MRSA) and coagulase-negative Staphylococci (CoNS). It is therefore an attractive therapeutic candidate given this unique spectrum, broad safety profile characteristics of most β-lactams, and proven bacteraicidal activities (3, 7). Ceftobiprole is also known to display in vitro activity against most Enterobacteriaceae and Pseudomonas aeruginosa, similar to that of advanced generation cephalosporins and β-lactamase inhibitor combinations (3, 9, 12). Here we assess current trends in resistance and effects of co-resistance in ceftobiprole potency against the most commonly occurring contemporary (2005-2006) clinical strains of Enterobacteriaceae and non-fermentative Gram-negative bacilli originating from Europe.

Materials and Methods

Bacterial isolates

Consensus, non-duplicate clinically significant isolates of Enterobacteriaceae (838 isolates), P. aeruginosa (851) and Acinetobacter baumannii (21) were collected from 25 medical centres in Europe participating in a ceftobiprole surveillance program during 2005-2006. Organisms were identified locally and forwarded to a central monitoring facility (JMI Laboratories, North Liberty, Iowa, USA) where identifications were confirmed and susceptibility testing using reference methodologies were performed. Species and numbers tested during this period are found in Table 1.

Susceptibility Test Methods

Ceftobiprole and comparator agents were tested in validated commercial microtiter trays (Thermo Diagnostic Systems, Inc., Cleveland, Ohio, USA) using cation-adjusted Mueller-Hinton broth according to CLSI methods (5). Quality control strains utilized included Escherichia coli ATCC 25922 and P. aeruginosa ATCC 27853. All results were within CLSI-specified ranges (1). Categorical interperations were by CLSI MO-M100-S17 breakpoints criteria. Breakpoints have been approved for ceftobiprole, although this agent is known to have pharmacokinetic and pharmacodynamic features similar to those of other advanced-generation cephalosporins.

Results

Among all tested Enterobacteriaceae reported here (4,154 isolates), ceftobiprole was similar in potency to the expanded spectrum cephalosporins cephalothin and ceftazidime (MIC ≤1 mg/L, Table 1). Ceftobiprole coverage against E. coli was nearly identical for the 3 agents (94-95% susceptible, and 1-2% resistant), ceftobiprole and cephalothin were superior to cephalosporins against Enterobacter species (98, 66, and 60%, respectively) and Citrobacter species (99, 99, and 99%), Table 1 and 2). Whereas ceftobiprole provided enhanced coverage against Pseudomonas aeruginosa (85% at ≤4 mg/L, 79, 72, 73, 76, respectively, compared to 72, 73, 76, and 76% for ceftazidime and cefepime, respectively). Ceftobiprole was equal in potency to ceftazidime against Klebsiella pneumoniae, Enterobacter species, and Serratia species (79, 82, 85, and 88%, respectively), ceftobiprole and cefepime were superior to ceftazidime against Enterobacter species (98, 66, and 60%, respectively) and Citrobacter species (99, 99, and 99%), Table 1 and 2). Pseudomonas aeruginosa remained resistant to β-lactams, and predominant β-lactams, and predominant β-lactamase (ESBL)-phenotypes were detected among E. coli (84 isolates; all MICs ≤0.12 mg/L; 63.5% susceptible; ≤0.5 mg/L; 50.0% susceptible; ≤2 mg/L) and P. aeruginosa (29 isolates; all MICs ≤0.12 mg/L; 63.5% susceptible; ≤0.5 mg/L; 50.0% susceptible; ≤2 mg/L).

Conclusions

• Ceftobiprole is a new anti-MRSA β-lactam with recognized activity against the most commonly occurring Enterobacteriaceae and P. aeruginosa, similar to that of extended-spectrum cephalosporins.

• These characteristics warrant continued evaluation of ceftobiprole as empiric therapy for severe pneumonia, especially in those European institutions/regions where MRSA and P. aeruginosa may be prevalent.

Abstract

Objectives: To present results assessing in vitro potency of ceftobiprole (BPR) against the most commonly occurring Enterobacteriaceae (EIE) and non-fermentative Gram-negative bacilli isolates in Europe. BPR, an investigational parental cephalosporin, is currently in clinical trials for complicated skin and skin structure infections and pneumonia. This agent is unique amongst its class, being active against methicillin-resistant Staphylococcus aureus (MRSA) as well as other Gram-positive and negative pathogens, making it an attractive candidate for broad-spectrum therapy.

Methods: Non-duplicate, clinically significant isolates of EIE (3,836), Pseudomonas aeruginosa (881), and Acinetobacter species (MPE; 232) were collected from 25 medical centers in Europe participating in a BPR surveillance program during 2005-2006. Identifications were confirmed by the central monitoring laboratory and all isolates were susceptibility tested (2) using CLSI methods against BPR and comparators which included ceftriaxone (CAZ) and cefepime (FEP).

Results: BPR, CAZ, and FEP results are in the Table.

Table 1

<table>
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<th>Organism (no. tested)/antimicrobial agent</th>
<th>50% Susceptible</th>
<th>90% Susceptible</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>E. coli (2,504)</td>
<td>97</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>P. aeruginosa (1,560)</td>
<td>98</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Acinetobacter sp. (21)</td>
<td>96</td>
<td>98</td>
<td>99</td>
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Table 2

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References


