The Novel β-lactamase Inhibitor ETX1317 Effectively Restores the Activity of Celpodoxime Against Extended Spectrum β-lactamase (ESBL)- and Carbapenemase-producing Enterobacteriaceae Isolated From Recent Urinary Tract Infections

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Abstract
The treatment of urinary tract infections (UTIs) has been complicated by the emergence of multi-drug resistant β-lactamases (BL)-expressing pathogens. ETX1317 is a novel diazabicyclooctene (DBOC) prodrug that is hydrolyzed in vivo to release the active inhibitor ETX1317. ETX1317 is in clinical development as an oral prodrug which is combined with cefpodoxime, a β-lactam antibiotic, to provide a novel combination therapy with a broad spectrum of activity against a wide range of Gram-negative Enterobacteriaceae. The current study was conducted to evaluate the activity of cefpodoxime combined with ETX1317 against ESBL- and carbapenemase-producing Enterobacteriaceae isolated from recent urinary tract infections (UTIs) in North America.

Background
Enterobacteriaceae are the leading cause of Gram-negative bloodstream infections in the USA [1,2]. The clinical impact of infections caused by β-lactamase (BL)-expressing pathogens is highlighted by the need for empirical treatment with agents that are effective against ESBL- and carbapenemase-producing Enterobacteriaceae (CPDPs) [3]. The study organisms included 126 clinical isolates, which were isolated from 2015-2016 from patients with infections caused by ESBL-producing and/or carbapenemase-producing Enterobacteriaceae in North America.

Methods
To determine the susceptibility of these clinical isolates to cefpodoxime and ETX1317, broth microdilution (BMD) testing was performed (CLSI M100, 28th Edition). Summary statistics were determined using SAS and Excel.

Results
A total of 126 ESBL-producing and/or carbapenemase-producing Enterobacteriaceae were evaluated in this study. The majority of organisms were species of Enterobacteriaceae, with 63% of isolates identified as Enterobacteriaceae, followed by Pseudomonas aeruginosa (11%) and Klebsiella pneumoniae (8%). The MICs of cefpodoxime alone and the combination of cefpodoxime plus ETX1317 were determined for each isolate. The combination was found to be synergistic in all isolates, as defined by CLSI guidelines, when compared to the individual MICs of the agents.

Conclusions
The combination of cefpodoxime and ETX1317 could represent a novel treatment for infections caused by ESBL- and/or carbapenemase-producing Enterobacteriaceae.

A Broad-spectrum Oral β-lactamase Inhibitor Combination

ETX1317 is a novel prodrug with activity against class B β-lactamase. ETX1317 also has intrinsic antibacterial activity against some Gram-negative bacteria.

The combination of cefpodoxime and ETX1317 was found to be synergistic in all isolates, as defined by CLSI guidelines, when compared to the individual MICs of the agents.

Introduction
35% of UTIs are caused by Enterobacteriaceae, which are the leading cause of Gram-negative bloodstream infections in the USA [1,2]. These pathogens are often resistant to multiple antibiotics, with ESBL-producing and/or carbapenemase-producing strains of Enterobacteriaceae being of particular concern in the hospital setting.

Activity of Cefpodoxime-ETX1317 by Bacterial Species

<table>
<thead>
<tr>
<th>Bacteriaceae Class</th>
<th>Beta-lactamase Class</th>
<th>β-Lactamase Inhibitor Combination</th>
<th>N</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>ESBL</th>
<th>MBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>Beta-lactamase Class</td>
<td>CPD + ETX1317</td>
<td>126</td>
<td>0.07</td>
<td>0.12</td>
<td>4/1</td>
<td>0/1</td>
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Isolates with Lower Susceptibility to Cefpodoxime-ETX1317

- 12 isolates with MIC values of 4 mg/L or greater were isolated from patients with disseminated infections, including 12 isolates with MICs ≥ 4 mg/L or greater for CRE. The MICs of these isolates were then determined for cefpodoxime alone and the combination of cefpodoxime plus ETX1317.
- Four of the 12 isolates were found to be resistant to the combination of cefpodoxime and ETX1317, with MIC values of ≥ 4 mg/L for CRE. These isolates were tested for the presence of ESBL and MBL.

Conclusions
ETX1317 is an oral prodrug with a broad spectrum of activity against ESBL- and/or carbapenemase-producing Enterobacteriaceae. The combination of cefpodoxime and ETX1317 could provide a novel treatment for infections caused by ESBL- and/or carbapenemase-producing Enterobacteriaceae.

References

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