In Vitro Activity of Cefpodoxime Proxetil (U-76,252; CS-807) against Clinical Isolates of Branhamella catarrhalis

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Cefpodoxime proxetil (U-76,252; CS-807) is a new esterified oral cephalosporin antibiotic with a broad antibacterial spectrum. Since data regarding the activity of cefpodoxime against Branhamella catarrhalis are limited, we tested its activity against 200 B. catarrhalis isolates. The drug was highly active against β-lactamase-negative and -positive isolates; 99% of all strains tested showed a cefpodoxime proxetil MIC of ≤2.0 μg/ml.

Cefpodoxime proxetil (U-76,252; CS-807) is a new esterified oral cephalosporin antibiotic with a wide spectrum of activity against gram-positive and gram-negative bacteria (3, 8, 11). After ingestion, it is absorbed from the gastrointestinal tract and undergoes hydrolysis to release the active form of the drug, U-76,253 or R-3763 (8). Pharmacokinetic studies to date demonstrate a cefpodoxime half-life in serum of 1.8 to 1.9 h and peak levels in serum in the 2- to 3-μg/ml range after a 200-mg dose (3, 8; A. Saito, Program Abstract 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 665, 1987).

Although several studies show that cefpodoxime is associated with a broad spectrum of antibacterial activity (3, 8, 11), data regarding its activity against Branhamella catarrhalis are somewhat limited. Results available thus far reveal B. catarrhalis susceptibility to cefpodoxime in the MIC range of 0.06 to 1.0 μg/ml (3, 8; B. H. Yagi and G. E. Zurenko, 27th ICAAC, abstr. no. 657, 1987). Since B. catarrhalis has emerged as a major respiratory pathogen (7) and, in fact, is the leading cause of purulent exacerbations of chronic bronchitis at the Mountain Home Veterans Administration Medical Center (unpublished observations), we undertook the present study to evaluate the in vitro activity of cefpodoxime compared with those of other orally administered antimicrobial agents against 200 of our B. catarrhalis isolates.

Bacterial strains. A total of 200 B. catarrhalis isolates were recovered from individual patients with lower respiratory tract infections at the Mountain Home Veterans Administration Medical Center in Johnson City, Tenn. Organisms were identified as B. catarrhalis according to Gram stain characteristics (gram-negative diplococci), oxidase production, growth on 5% sheep blood agar incubated at 37°C in a 10% CO2 environment, lack of pigmentation, lack of fermentation of glucose, maltose, or sucrose, and production of DNase (4). Each isolate underwent analysis for β-lactamase production by using the chromogenic cephalosporin disk nitrocefin (Cefinase; BBL Microbiology Systems, Cockeysville, Md.).

Antimicrobial agents. The in vitro evaluation of cefpodoxime proxetil (U-76,252; CS-807) was conducted by using U-76,253A (R-3746), which is the active metabolite sodium salt of the pro-drug ester. The U-76,253A was provided by The Upjohn Co., Kalamazoo, Mich. Other antimicrobial agents used for comparison (ampicillin, amoxicillin-clavulanic acid, cephalixin, cefaclor, cefuroxime, erythromycin, tetracycline, and trimethoprim-sulfamethoxazole) were supplied by their respective manufacturers in the United States.

Susceptibility testing. A broth microdilution method with cation-supplemented Mueller-Hinton broth was used to determine MICs. The MIC 2000 instrument (Dynatech Laboratories, Inc., Alexandria, Va.) was used in the preparation and inoculation of microdilution plates. An inoculum of 105 CFU/ml was employed, and MICs were determined as the lowest concentration of antibiotic at which no visible growth was noted after 18 to 24 h of incubation at 35°C. Quality control testing was carried out with Staphylococcus aureus ATCC 29213, Escherichia coli ATCC 25922, and E. coli ATCC 35218 (9).

Similar to previously reported findings from our facility (1), a total of 160 (80%) of the 200 B. catarrhalis isolates were β-lactamase positive.

In Table 1, the activity of cefpodoxime proxetil in the form of U-76,253A and eight other oral antibiotics against 40 β-lactamase-negative and 160 β-lactamase-positive B. catarrhalis isolates is summarized. At a proposed MIC breakpoint of ≤2.0 μg/ml, cefpodoxime proved to be highly active against both β-lactamase-negative and -positive organisms. For only two (1.25%) of the 160 β-lactamase-positive group was the cefpodoxime MIC ≥3.2 μg/ml. The eight other antibiotics showed a good level of activity against β-lactamase-negative isolates, with amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole being most active in this group. These latter two agents maintained their high degree of activity even among the β-lactamase-positive isolates. Others have shown that the β-lactamases of B. catarrhalis are highly susceptible to clavulanic acid and that the amoxicillin MICs for β-lactamase-positive strains can be reduced to values seen among non-enzyme-producing strains by the addition of 0.5 to 1.0 μg of clavulanic acid per ml (6, 12). Ampicillin was not reliably active against the β-lactamase-producing strains; 18% showed ampicillin MICs of ≥4.0 μg/ml. Although therapeutic success has been noted with the use of ampicillin in the treatment of β-lactamase-producing strains of B. catarrhalis, it seems appropriate to avoid the use of ampicillin in this setting (10). A reevaluation of interpretive criteria used for ampicillin susceptibility testing may further clarify the activity of this drug against various strains of B. catarrhalis (2). Finally, it should be noted that the MICs for 90% of the β-lactamase-producing strains were higher for all β-lactam agents except cephalixin. In this

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regard, it is acknowledged that β-lactamase instability may not always be reflected by MICs in the resistant range.

Overall, our results with antimicrobial agents other than cefpodoxime are consistent with those of Doern and Tubert (5). With regard to the in vitro activity of cefpodoxime against *B. catarrhalis*, our data expand considerably upon the findings of Yagi and Zurenko (27th ICAAC) and others (3, 8), who evaluated small numbers of *B. catarrhalis* isolates and in certain instances did not clarify the β-lactamase activity associated with the tested strains. The results of the present study confirm a high level of activity of cefpodoxime against both β-lactamase-negative and -positive isolates of *B. catarrhalis*. Using a proposed MIC breakpoint of ≤2.0 μg/ml, 99% of all tested isolates and 98.8% of β-lactamase-positive isolates were susceptible to cefpodoxime.

In view of the reported in vitro activity of cefpodoxime against *Streptococcus pneumoniae* and *Haemophilus influenzae* (both β-lactamase-negative and -positive isolates) (3, 8) and our data confirming its activity against a substantial number of *B. catarrhalis* isolates, cefpodoxime may have a role in the treatment of certain respiratory tract infections caused by these pathogens.

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**LITERATURE CITED**


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**TABLE 1. Activity of U-76,253A and other antimicrobial agents against 200 *B. catarrhalis* isolates**

<table>
<thead>
<tr>
<th>Antimicrobial agent*</th>
<th>MIC (μg/ml)*&lt;sup&gt;b&lt;/sup&gt; for:</th>
<th>β-Lactamase-negative isolates (n = 40)</th>
<th>β-Lactamase-positive isolates (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>90%</td>
<td>Range</td>
</tr>
<tr>
<td>U-76,253A</td>
<td>0.1</td>
<td>0.2</td>
<td>≤0.025-0.4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>≤0.125</td>
<td>0.25</td>
<td>≤0.125-4.0</td>
</tr>
<tr>
<td>Amox-clav</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td>≤0.06-1.0</td>
</tr>
<tr>
<td>Cephalixin</td>
<td>2.0</td>
<td>4.0</td>
<td>2.0-4.0</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.25</td>
<td>0.5</td>
<td>≤0.125-1.0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>≤0.25</td>
<td>0.5</td>
<td>≤0.25-1.0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.25</td>
<td>0.5</td>
<td>≤0.06-0.5</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.5</td>
<td>1.0</td>
<td>0.25-2.0</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>≤0.125</td>
<td>≤0.125</td>
<td>≤0.125-0.25</td>
</tr>
</tbody>
</table>

* U-76,253A, Sodium salt of the active metabolite of U-76,252 (CS-807) pro-drug ester; Amox-clav, amoxicillin-clavulanic acid combination tested at a ratio of 2:1 (only the amoxicillin data are shown); TMP-SMX, trimethoprim and sulfamethoxazole combined at a ratio of 1:19 (only the trimethoprim data are shown).

<sup>b</sup> 50% and 90%, MICs for 50 and 90% of the isolates, respectively.