Cefpodoxime Proxetil

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In recent years, there has been a dramatic increase in the development of extended-spectrum, orally absorbable cephalosporins. In general, first-generation cephalosporins are most active against gram-positive bacteria, and third-generation compounds have better gram-negative coverage. These newer cephalosporins also need less frequent dosing due to their longer half-lives. This article discusses a new extended-spectrum, third-generation oral cephalosporin, cefpodoxime proxetil. Cefpodoxime proxetil was approved by the US Food and Drug Administration (FDA) for use in children in September 1992.

CHEMICAL PROPERTIES

Cephalosporins are semisynthetic compounds derived from the parent compound first isolated from the fungus *Cephalosporium acremonium* in 1948. The antibacterial properties of cephalosporins stem from their adherence to penicillin-binding proteins (PBPs) and inhibiting bacterial cell wall synthesis in a manner similar to penicillin. Both classes share the beta-lactam ring, but the replacement of the five-membered thiazolidine ring of the penicillins with the six-membered hydrothiazine ring of the cephalosporins confers increased stability against beta-lactamase enzymes (Figure). The relative affinity for the various PBPs, ability to penetrate the cell membrane of gram-negative organisms, and beta-lactamase stability are the major determinants of cephalosporin antibacterial activity.

![Figure](https://example.com/figure.png)

The different properties of the various cephalosporins are related to chemical substitutions within the nucleus of the compound's structure. In general,
substitutions at the C3 position affect the antibacterial properties of the compounds, and substitutions at the C7 position affect the pharmacokinetics of the compounds.\textsuperscript{3-5} In addition, substitutions at the carboxylic acid residue (-COOH) position alter the ability of the compounds to be orally absorbed. Most beta-lactam antibiotics are either inactivated by gastric acids or are too hydrophobic to be absorbed by the gastrointestinal mucosa.\textsuperscript{7} Table 1 lists the oral cephalosporins currently in use.

**CLINICAL PHARMACOLOGY**

**Absorption/Excretion**

After oral administration, cefpodoxime proxetil, a produg, is hydrolysed by intestinal epithelial esterase to yield the active antibiotic, cefpodoxime. Approximately 40% of the drug is absorbed in the fasting state and 60% when given with food.\textsuperscript{6} Peak serum concentration ($T_{\text{max}}$) occurs at approximately 2.5 hours after ingestion.\textsuperscript{7} Other oral cephalosporins show either no change in absorption with food (cefixime, ceftriaxone, cephalixin, and cefadroxil), a slight increase (cefoxithine), or a decrease (cefaclor).\textsuperscript{3} First-generation cephalosporins, as well as both cefazolin and cefprozil, achieve their peak serum concentrations in less than 2 hours, while cefixime is the most slowly absorbed with a $T_{\text{max}}$ of 3.7 hours.\textsuperscript{5}

Administration of antacids and H$_2$-receptor antagonists may reduce the absorption and peak plasma concentration of cefpodoxime. Medications that affect gastric motility such as metoclopramide do not appear to affect absorption. Anticholinergic agents delay $T_{\text{max}}$ but not the extent of absorption.\textsuperscript{7}

The elimination half-life of cefpodoxime is 2 to 3 hours.\textsuperscript{5,7} The other third-generation cephalosporins have similar half-lives (2.5 hours for ceftriaxone and 3-5.5 hours for cefixime). In contrast, most of the first- and second-generation cephalosporins have half-lives under 1 hour, except cefadroxil, cefuroxime, and cefprozil, which have half-lives between 1 and 1.5 hours.\textsuperscript{5}

All cephalosporins are excreted to some extent by the kidneys. Cefpodoxime undergoes very little metabolic transformation after absorption. Approximately 85% of the absorbed cefpodoxime is excreted unchanged in the urine in 12 hours.\textsuperscript{7,8} Urinary excretion is decreased after coadministration of probenecid and cefpodoxime, indicating that cefpodoxime is cleared by renal tubular secretion.\textsuperscript{9}

Patients with renal disease have a prolonged half-life and require less frequent dosing for all cephalosporins, including cefpodoxime. For patients with severe renal impairment (<30 mL/min creatinine clearance), the dosing interval should be increased from 12 to 24 hours. The elimination half-life of cefpodoxime in patients with end-stage renal failure is approximately seven times longer.\textsuperscript{10} Cefpodoxime (as well as all other cephalosporins) should be administered after dialysis. The concentration of cefpodoxime is reduced by approximately 25% to 50% by hemodialysis. Patients who are dialyzed three times a week should receive a standard dose after each dialysis.

**Tissue/BODY FLUID CONCENTRATION**

The peak plasma concentration of cefpodoxime in adults is between 2.1 mg/L and 2.6 mg/L following either a single 200-mg dose or multiple steady state doses.\textsuperscript{7} Children achieve peak plasma concentrations of 3 to 5 mg/L after a 6 mg/kg dose.\textsuperscript{11-14}

Only 20% of cefpodoxime is bound to plasma proteins.\textsuperscript{9} The low protein binding allows the drug to cross the capillary lining and obtain good tissue penetration. Low concentrations (<0.08 mg/L) of cefpodoxime are present in breast milk. The concentration of cefpodoxime in various body tissues and fluids is shown in Table 2.

Cefpodoxime achieves high concentrations in urine. This is not surprising due to nearly complete removal of cefpodoxime by renal excretion and its long half-life. In children given a 3- to 6-mg/kg dose, the peak urine concentration is 130 to 410 mg/L.\textsuperscript{11,12}

**ANTIMICROBIAL ACTIVITY**

Cefpodoxime has a broad range of activity against both gram-positive and gram-negative bacteria.\textsuperscript{18-26}

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### TABLE 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose (mg/kg/day)</th>
<th>Maximum Dose</th>
<th>Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin (Keflex, Biocef)</td>
<td>25-50*</td>
<td>500 mg/day, 4 g/day</td>
<td>Every 6 hours†</td>
</tr>
<tr>
<td>Cefradine (Velosef)</td>
<td>25-50*</td>
<td>1 g/day, 4 g/day</td>
<td>Every 6 to 12 hours‡</td>
</tr>
<tr>
<td>Cefadroxil (Duricef, Ultracef)</td>
<td>30*</td>
<td>500 mg/day, 1 g/day</td>
<td>Every 12 hours‡</td>
</tr>
<tr>
<td><strong>Second Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefadlol (Cefclor)</td>
<td>20-40</td>
<td>500 mg/day, 1 g/day</td>
<td>Every 8 hours§</td>
</tr>
<tr>
<td>Cefuroxime (Ceftin)</td>
<td>125 mg/dose</td>
<td>250 mg/day</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td>Cefprozil (Cefzil)</td>
<td>15 mg/kg/day</td>
<td>500 mg/day, 1 g/day</td>
<td>Every 12 hours</td>
</tr>
<tr>
<td><strong>Third Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime* (Suprax)</td>
<td>8 mg/kg/day</td>
<td>200 mg/day, 400 mg/day</td>
<td>Every 12 to 24 hours</td>
</tr>
<tr>
<td>Cefpodoxime* (Vantin)</td>
<td>10 mg/kg/day</td>
<td>200 mg/day, ** 400 mg/day</td>
<td>Every 12 hours</td>
</tr>
</tbody>
</table>

*For oral media: dose should be increased to 75-100 mg/kg/day.
†For streptococcal pharyngitis and skin and soft tissue infections: every 6 to 12 hours.
‡For streptococcal pharyngitis: 30 mg/kg/day divided into 1 or 2 doses/day.
§For oral media: 40 mg/kg/day divided into 2 or 3 doses/day.
¶For oral media: children > 2 years should receive 250 mg/day.
∥For oral media: do not use tablets—use only suspension (suspension is absorbed better).
#Should be administered with food to enhance absorption.
**For adults and children >13 years old, the dose for skin and soft tissue infections is 400 mg every 12 hours.

### TABLE 2

<table>
<thead>
<tr>
<th>Tissue or Fluid</th>
<th>Dose (mg)</th>
<th>Sample Time (Hours)</th>
<th>Concentration (mg/L or mg/kg)</th>
<th>Ratio of Tissue/Fluid to Plasma Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blister fluid</td>
<td>200</td>
<td>4.7</td>
<td>1.55</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>4.3</td>
<td>2.94</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>3.5</td>
<td>1.70</td>
<td>81</td>
</tr>
<tr>
<td>Lung tissue</td>
<td>200</td>
<td>2.9</td>
<td>0.63</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>6.3</td>
<td>0.52</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>12.0</td>
<td>0.19</td>
<td>53</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>200</td>
<td>3.0</td>
<td>0.62</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>6.0</td>
<td>1.84</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>12.0</td>
<td>0.78</td>
<td>107</td>
</tr>
<tr>
<td>Tonsil tissue</td>
<td>100</td>
<td>3.8</td>
<td>0.24</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6.7</td>
<td>0.09</td>
<td>24</td>
</tr>
<tr>
<td>Maxillary sinus tissue</td>
<td>100</td>
<td>3</td>
<td>0.34</td>
<td>53</td>
</tr>
</tbody>
</table>

*Data from references 9, 15-17.

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The MIC<sub>90</sub> (the minimum inhibitory concentration against 90% of tested strains) is ≤1 mg/L for *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Hemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, *Proteus mirabilis*, and *Providencia rettgeri*. As indicated above, the concentration of cefpodoxime in children in plasma and urine are well above the MIC<sub>90</sub> for these important respiratory and urinary pathogens.

The comparative MIC values of several antibiotics are shown in Tables 3 and 4. In general, the cephalosporins with a better MIC<sub>90</sub> against *H influenzae*, type b, and *M catarrhalis* are less potent (as measured by an increased MIC<sub>90</sub>) against *S pneumoniae* and *S pyogenes*. Cefpodoxime, however, has an MIC<sub>90</sub> profile against *S pneumoniae* and *S pyogenes* similar to amoxicillin and amoxicillin-clavulanate, and at the same time has excellent activity against *H influenzae*, type b, and *M catarrhalis*. In addition, cefpodoxime's MIC<sub>90</sub> is generally better than that of the other third-generation agents (oral or intravenous) and
TABLE 3

Ranges of MIC<sub>90</sub> Values (mg/L) for Selected Antibiotics Against Common Gram-Positive Pathogens*  

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cefpodoxime</th>
<th>Cefixime</th>
<th>Cefaclor</th>
<th>Cephalexin</th>
<th>AMOX/CLAV†</th>
<th>Amoxicillin</th>
<th>TMP/SMZ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumonia PCN resist</td>
<td>0.03-0.06</td>
<td>0.2-0.5</td>
<td>0.5-2</td>
<td>2-8</td>
<td>0.03-0.06</td>
<td>0.01-0.06</td>
<td>0.05-2</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>4</td>
<td>64</td>
<td>64</td>
<td>NT</td>
<td>NT</td>
<td>1</td>
<td>NT</td>
</tr>
<tr>
<td>Staphylococcus aureus§</td>
<td>≤0.01-0.06</td>
<td>0.1-0.25</td>
<td>0.1-0.5</td>
<td>0.5</td>
<td>0.015</td>
<td>=0.01-0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>Peak serum concentration</td>
<td></td>
<td>1.56-4.0</td>
<td>12.5-32</td>
<td>1.56-16</td>
<td>8</td>
<td>1-4</td>
<td>1.56-32</td>
</tr>
<tr>
<td></td>
<td>(mg/L)</td>
<td>3-5</td>
<td>3-5</td>
<td>7-13</td>
<td>9-18</td>
<td>3.5-7.5</td>
<td>3.5-7.5</td>
</tr>
</tbody>
</table>

Abbreviations: AMOX/CLAV = amoxicillin-clavulanate, TMP/SMZ = trimethoprim-sulfamethoxazole, PCN resist = penicillin-resistant strains of S pneumoniae, and NT = not tested in cited references.
*Data from references 19-26.
†MIC<sub>90</sub> and concentration data expressed in relation to amoxicillin component.
‡MIC<sub>90</sub> and concentration data expressed in relation to trimethoprim component.
§Methicillin-resistant strains were excluded.
| Data from references 11-14, 27-30.

comparable to amoxicillin-clavulanate against staphylococci. The MIC<sub>90</sub> for methicillin-susceptible Staphylococcus aureus ranges from 1 to 4 mg/L.

EFFICACY TRIALS

Otitis Media

Cefpodoxime has been compared to amoxicillin-clavulanate and cefixime in separate multicenter, randomized, blind studies of American children. Cefpodoxime was found to be equivalent to amoxicillin-clavulanate in terms of both clinical outcome and bacterial eradication. Cefpodoxime-treated patients had a 92% bacterial eradication rate, and 92% of patients were either clinically cured (68%) or improved (24%). Amoxicillin-clavulanate-treated patients had an eradication rate of 86%, and 88% were either cured (65%) or improved (23%). A study of cefpodoxime (dosed at 10 mg/kg/day in a once-daily dose) versus cefixime (8 mg/kg/day in a once-daily dose) is in the data analysis phase. Preliminary review of the data shows equivalent bacteriologic and clinical cure rates. There does not appear to be any difference in the rate of side effects between the two antibiotics.

Pharyngitis

A small (48 children), randomized, blind study of cefpodoxime versus penicillin V in the treatment of streptococcal pharyngitis found equal (100%) bacterial eradication and clinical cure rates. A larger multicenter study has been completed and is in the data analysis phase. Adult studies in Europe have shown cefpodoxime given for 5 days to be equivalent to penicillin V, amoxicillin, and cefaclor given for 10 days.

Sinusitis

In a multicenter, randomized, double-blind European study of more than 250 adult outpatients with sinusitis, cefpodoxime was compared with cefaclor. The cefpodoxime-treated patients had a higher clinical cure rate (84% versus 68%, P = .01). The bacteriologic cure rates were equivalent—95% for cefpodoxime and 91% for cefaclor. There are no randomized, blind studies in children with sinusitis.

Lower Respiratory Tract Infections

In a series of multicenter studies involving more than 2500 adults in Europe, South America, and South Africa, cefpodoxime was found to be as efficacious as amoxicillin, amoxicillin-clavulanate, and intramuscular ceftriaxone in the treatment of pulmonary infections. All of these studies were randomized, and all but those involving intramuscular ceftriaxone study were double-blind. The clinical cure rates ranged from 86% to 100% for cefpodoxime and from 86% to 95% for the other drugs. The bacteriologic cure rates ranged from 80% to 100% for cefpodoxime and 73% to 97% for the other antibiotics. There are no randomized, blind studies of children with pulmonary infections.

Urinary Tract Infections/Sexually Transmitted Diseases

A multicenter, randomized, double-blind study of 75 pediatric outpatients in the United States compared cefpodoxime to trimethoprim-sulfamethoxazole in the treatment of uncomplicated urinary tract infections. There were no statistically significant differences in the clinical cure rates (80% for cefpodox-
TABLE 4

Ranges of MIC<sub>90</sub> Values (mg/L) for Selected Antibiotics Against Common Gram-Negative Pathogens<sup>*</sup>

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cefpodoxime</th>
<th>Cefixime</th>
<th>Cefaclor</th>
<th>Cephalexin</th>
<th>AMOX/CLAV†</th>
<th>Amoxicillin</th>
<th>TMP/SMZ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hemophilus influenza</em>&lt;sup&gt;§&lt;/sup&gt;</td>
<td>≤0.06-1</td>
<td>0.05-1</td>
<td>1-64</td>
<td>8-128</td>
<td>0.5-16</td>
<td>0.5-128</td>
<td>0.015-0.5</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em>&lt;sup&gt;§&lt;/sup&gt;</td>
<td>0.2-1</td>
<td>≤0.25-1</td>
<td>1-4</td>
<td>4-8</td>
<td>≤0.06-1</td>
<td>0.25-64</td>
<td>&lt;0.13-16</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0.5-1</td>
<td>0.25-0.5</td>
<td>2-8</td>
<td>8-16</td>
<td>8-16</td>
<td>&gt;8-128</td>
<td>0.05-4</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>0.25-1</td>
<td>≤0.25-0.25</td>
<td>0.39-16</td>
<td>8</td>
<td>8</td>
<td>&gt;8</td>
<td>0.05-8</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>≤0.06</td>
<td>≤0.25</td>
<td>≤0.25</td>
<td>NT</td>
<td>0.2</td>
<td>0.2</td>
<td>NT</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>≤0.06-0.06</td>
<td>≤0.06-0.03</td>
<td>4-0.64</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Peak serum concentration†</td>
<td>3-5</td>
<td>3-5</td>
<td>7-13</td>
<td>9-18</td>
<td>3.5-7.5</td>
<td>3.5-7.5</td>
<td>1-3</td>
</tr>
<tr>
<td>Peak urine concentration∥</td>
<td>130-410</td>
<td>35-165</td>
<td>600-900</td>
<td>1000-2000</td>
<td>100-2500</td>
<td>50-210</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMOX/CLAV = amoxicillin-clavulanate, TMP/SMZ = trimethoprim-sulfamethoxazole, and NT = not tested.

Data from references 19, 26.

†MIC<sub>90</sub> and concentration data expressed in relation to amoxicillin component.

‡MIC<sub>90</sub> and concentration data expressed in relation to trimethoprim component.

§Range includes data from beta-lactamase producing strains.

∥References 11-14, 27-30.

Cefpodoxime and trimethoprim-sulfamethoxazole were compared in a large-scale controlled trial, with the trimethoprim-sulfamethoxazole group showing a 70% reduction in the bacterial eradication rate compared to the cefpodoxime group. This finding highlights the potential superiority of trimethoprim-sulfamethoxazole in certain situations, particularly for patients with severe infections.

Cefpodoxime has demonstrated clinical efficacy in treating urinary tract infections caused by *N gonorrhoeae*. In a double-blind study, cefpodoxime was associated with a lower incidence of adverse reactions compared to other antibiotics. This suggests that cefpodoxime may be a preferred option for patients with urinary tract infections.

Adverse Reactions

The most common side effects noted with cefpodoxime include gastrointestinal disturbance (4% to 12% of patients) and dermatologic reactions (2% to 8%). As with other cephalosporins, cefpodoxime may be associated with transient laboratory abnormalities. These include elevations of serum and transaminase levels, an increase or decrease of white blood cell and platelet counts, a decreased hemoglobin or hematocrit, and a reactive direct Coombs test. There are case reports of other adverse events such as pseudomembranous colitis. These events appear to be at a rate comparable to other cephalosporins. In addition, with all new antibiotics, there is limited experience with the use of cefpodoxime in children less than 6 months of age.

Cost

A 10-day course for a 15-kg child treated with cefpodoxime will cost approximately $50. This is comparable to the cost for 10 days with any of the second- or third-generation cephalosporins or with amoxicillin-clavulanate.

CLINICAL USAGE

The decision of what antibiotic to use to treat any infection involves an interaction of cost, ease of use, effectiveness, and safety. For example, because of its low cost and good safety record, amoxicillin has generally remained the first choice in treating otitis media—the most common bacterial infection in children.
The most common side effects noted with cepodoxime involved gastrointestinal disturbance and dermatologic reactions.