Activity of Once-Daily Cefpodoxime Regimens against Haemophilus influenzae and Streptococcus pneumoniae with an In Vitro Pharmacodynamic Chamber Model

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To characterize the in vitro effectiveness of once-daily dosing with cefpodoxime against Haemophilus influenzae and Streptococcus pneumoniae infections, an in vitro pharmacodynamic chamber model was used to compare the bacterial killing activities of three cefpodoxime regimens: 100 mg twice daily (BID), 200 mg once daily (QD), and 400 mg QD. At the end of 24 h, the regrowth of H. influenzae isolates in the QD regimen was of concern, and the total logarithmic reduction was greatest in the BID regimen (3.1 log). Against S. pneumoniae isolates, the largest reductions in bacterial counts were observed in the 100-mg BID (5.5 log) and 400-mg QD (4.0 log) regimens. These data suggest that 400 mg of cefpodoxime given QD may have a role in the therapy of infections involving S. pneumoniae isolates.

Over the past several years, there has been a significant increase in the number of oral antibiotics, particularly beta-lactam agents (10, 16). Subsequently, newer antimicrobial agents must offer distinct therapeutic or pharmacokinetic advantages over existing agents. Cefpodoxime proxetil, approved for use in the United States approximately 3 years ago, has excellent activity against the majority of organisms associated with community-acquired infections (2, 5, 7, 9, 13). With the exception of single daily dosing for uncomplicated gonococcal infections, dosage recommendations for cefpodoxime have typically been twice daily. On the basis of promising results from clinical trials involving once-daily regimens (1), a suspension formulation of cefpodoxime recently received U.S. Food and Drug Administration approval for use as a single daily dose (10 mg/kg of body weight per day; maximum, 400 mg/day) for managing acute otitis media. The potential use of a single daily dose of cefpodoxime represents a significant advantage over the use of existing agents, many of which must be dosed on a more frequent basis.

To further define the potential use of once-daily cefpodoxime regimens against Haemophilus influenzae and Streptococcus pneumoniae infections, an in vitro pharmacodynamic chamber model capable of evaluating the influence of gradient antimicrobial concentrations on bacteria was used to accurately characterize the bacterial time-kill curves associated with three simulated cefpodoxime regimens. From these time-kill data, the total logarithmic reductions in bacterial counts by the three regimens at 24 h were determined and compared.

Cefpodoxime free acid was provided by the Upjohn Company (lot 102; 991 µg/ml; Kalamazoo, Mich.). The model was used to simulate dosage regimens of 100 mg every 12 h (100 BID), 200 mg every 24 h (200 QD), and 400 mg every 24 h (400 QD). The maximum cefpodoxime concentrations in serum (Cmax) obtained with these three regimens were 1.5, 2.4, and 4.1 µg/ml, respectively, and a drug elimination half-life (t1/2) of 2.5 h was used (3). A 1-µg/ml stock solution of cefpodoxime was prepared according to the manufacturer’s instructions, and aliquots were frozen at −70°C. Prior to each experiment, a frozen aliquot of stock solution was thawed at room temperature and thoroughly mixed. The area under the concentration-time curve from time zero to 24 h (AUC0–24) was calculated for each regimen. In addition, the percentage of time that the cefpodoxime concentrations exceeded the MIC during the 24-h experiments (T>MIC), and the ratio of the AUC0–24 to the MIC (AUC0–24/MIC) were determined from concentration-time data and the initial MICs for each isolate.

A type b, β-lactamase-producing isolate of H. influenzae (ATCC 33533) from blood and an isolate of S. pneumoniae from a clinical blood specimen were used. Their susceptibilities to cefpodoxime were determined in triplicate by macrodilution techniques according to the guidelines of the National Committee for Clinical Laboratory Standards (14). The in vitro model consisted of a tightly sealed, 280-ml glass chamber fitted with inflow, outflow, and sampling ports (11, 12). Haemophilus test medium supplemented with calcium and magnesium (14) and Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) were used as the growth media for the H. influenzae and S. pneumoniae isolates, respectively. On the day of each experiment, two to five isolated colonies were selected from 24-h subcultures, inoculated into fresh broth, and incubated at 34°C for approximately 2 to 4 h until the turbidity was equivalent to that of a McFarland 0.5 turbidity standard. A 1:55 dilution of this bacterial suspension was placed into the model to provide an approximate initial inoculum of 107 CFU/ml. After inoculation of the model, an appropriate volume of antibiotic stock solution was injected as a bolus to produce the desired Cmax on the basis of the dosage regimen being simulated. An additional bolus of antibiotic was delivered at 12 h for experiments evaluating the twice-daily regimen. To mimic the elimination characteristics of cefpodoxime in humans, a peristaltic pump continually delivered antibiotic-free medium into the model, which displaced an equal volume of medium containing drug. The flow rate of the pump was set to achieve the desired cefpodoxime t1/2. Prior studies have validated the ability of the model to accurately simulate the first-order elimination of antibiotic over time (11, 12). The temperature of the model was kept constant at 34°C with a water bath, and the medium was...
TABLE 1. Pharmacokinetic and pharmacodynamic parameters associated with cefpodoxime regimens

<table>
<thead>
<tr>
<th>Organism and regimens</th>
<th>Cmax (mg/liter)</th>
<th>AUC0–24 (mg · h/liter)</th>
<th>% T&gt;MIC</th>
<th>AUC0–24/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 BID</td>
<td>1.5</td>
<td>11.1</td>
<td>100</td>
<td>740</td>
</tr>
<tr>
<td>200 QD</td>
<td>2.5</td>
<td>9.7</td>
<td>76.3</td>
<td>647</td>
</tr>
<tr>
<td>400 QD</td>
<td>4.3</td>
<td>18.5</td>
<td>84.2</td>
<td>1,233</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 BID</td>
<td>1.6</td>
<td>11.8</td>
<td>100</td>
<td>393</td>
</tr>
<tr>
<td>200 QD</td>
<td>2.6</td>
<td>10.2</td>
<td>65.8</td>
<td>340</td>
</tr>
<tr>
<td>400 QD</td>
<td>4.3</td>
<td>19.3</td>
<td>73.8</td>
<td>643</td>
</tr>
</tbody>
</table>

Continuously mixed with magnetic stirring bars. To obtain a representative average bacterial time-kill curve, three independent experiments were conducted over a 24-h period for each regimen. In addition, 12-h controlled-growth experiments were performed to ensure the exponential growth of each isolate within the model.

To quantify the numbers of viable bacteria over time, 150-μl samples were aseptically taken initially and at selected intervals throughout the 24-h experiments and serially diluted, and 100-μl aliquots were immediately plated onto appropriate agar plates. The plates were incubated at 34°C with 5 to 7% CO₂ for 24 to 48 h. To minimize the possibility of antibiotic carryover, only plates with 10 to 300 CFU at a dilution of ≥1:50 were used in the analysis. The numbers of viable bacteria (the number of CFU per milliliter) were logarithmically plotted over time for triplicate experiments to determine the average bacterial time-kill curve for each cefpodoxime regimen. From these data, the total logarithmic decrease in the bacterial inoculum was determined. The lower limit of bacterial detection was 2.0 CFU/ml (log₁₀ scale). A Micrococcus luteus ATCC 9341 bioassay was used to determine the cefpodoxime concentrations in each sample (4).

The pharmacokinetic and pharmacodynamic parameters associated with each cefpodoxime regimen fell within an acceptable range (Table 1). Proportional changes were observed in AUC data as the total 24-h dose increased. Experimental AUC values also coincided with values reported from in vivo studies (3). Isolates were susceptible to cefpodoxime, with MICs of 0.015 μg/ml for the H. influenzae isolates and 0.03 μg/ml for the S. pneumoniae isolates. The BID regimens provided concentrations above the MIC throughout the entire 24-h duration. In contrast, the times above the MIC for H. influenzae and S. pneumoniae isolates were 76 and 66%, for the 200 QD regimens, respectively, and 84 and 74% for the 400 QD regimen, respectively. Because of the rather low MICs associated with each isolate, the calculated AUC0–24/MICs were relatively higher.

The initial inocula averaged 1.3 × 10⁶ CFU/ml for the H. influenzae experiments and 3.1 × 10⁶ CFU/ml for the S. pneumoniae experiments. Average bacterial time-kill curves for each regimen are illustrated in Fig. 1. In the absence of antibiotic, control growth experiments demonstrated the appropriate growth of each isolate in the chamber model. Against H. influenzae, all regimens produced pronounced bacterial killing during the initial 6 h, after which the time-kill curves began to plateau (Fig. 1A). The total logarithmic reductions in the numbers of H. influenzae isolates at the end of 24 h were 3.1, 0.4, and 0.5 for the 100 BID, 200 QD, and 400 QD regimens, respectively. Bacterial regrowth was observed in all regimens; however, the extent of H. influenzae regrowth was more pronounced with the QD regimens, coming within 0.5 log of the starting inoculum. Time-kill curve data for S. pneumoniae isolates were similar for each of the three regimens over the initial 12 h, with a >3 log₁₀ reduction in bacterial counts by 9 h (Fig. 1B). Regrowth of S. pneumoniae isolates was not observed until approximately 18 h, and total reductions in the numbers of bacteria were 5.5, 2.2, and 4.0 for the 100 BID, 200 QD, and 400 QD regimens, respectively. Similar to experiments with H. influenzae, regrowth was more prominent in the single-dose regimens; however, the 400 QD regimen had considerably less regrowth relative to that in the 200 QD regimen.

It has been well established that beta-lactam agents exhibit concentration-independent killing (6, 8, 15). Subsequently, the T>MIC for beta-lactams is recognized as an important pharmacodynamic parameter related to their antimicrobial efficacies. More specifically, maintaining concentrations above the MIC for an entire 24-h dosing period has been associated with maximal beta-lactam efficacy (18). Schentag and colleagues (17) have also advocated the ratio of AUC to MIC (AUC/MIC or AUIC) as a determinant of beta-lactam, quinolone, and aminoglycoside activities. In most cases, these two parameters are directly related; an increase in the AUC typically results in a greater duration of time above the MIC for the organism. During the initial portion of our experiments, the QD regimens appeared to be just as effective as the BID regimens.
However, by the end of 24 h the greatest reduction in the numbers of CFU per milliliter occurred in the BID regimens. The minimal regrowth and favorable time-kill curve patterns observed with the BID regimens were most likely due to the consistent maintenance of cefpodoxime concentrations above the MIC for each isolate. This certainly supports the importance of $T > \text{MIC}$ as a primary predictor of antimicrobial effectiveness. In contrast to previous reports (17), AUC/MICs far greater than those of the 100 BID and 200 QD regimens. Despite this impressively high AUC/MIC, the regrowth of both isolates occurred toward the end of 24 h, particularly in studies with the H. influenzae isolates. These data contradict the use of AUC/MIC as an accurate predictor of beta-lactam activity and suggest that $T > \text{MIC}$ is a more consistent indicator of activity.

The activity of cefpodoxime against the two study isolates differed. Both QD regimens had a similar degree of H. influenzae regrowth which approached the level of the starting inoculum. In comparison, the 400 QD regimen achieved more than a 2-log greater reduction in the S. pneumoniae starting inoculum relative to that achieved by the 200 QD regimen. In general, cefpodoxime demonstrated greater activity against the S. pneumoniae isolates. Although not specifically evaluated in our study, one possible explanation for the better time-kill curve patterns associated with the S. pneumoniae isolates may involve the postantibiotic effect (PAE) frequently observed between beta-lactams and gram-positive aerobes. Reports have suggested a cefpodoxime PAE of up to 4 h with S. pneumoniae isolates (9, 19), whereas little evidence exists to suggest that cefpodoxime has a PAE against H. influenzae isolates.

Extension of our experiments beyond 24 h to further assess regrowth and evaluation of additional S. pneumoniae and H. influenzae strains would provide a stronger basis for extrapolating these experimental data to the clinical setting. Despite these limitations, the in vitro pharmacodynamic model used in the present study provided results superior to those obtained by traditional susceptibility tests in which MICs are determined.

The primary purpose of the present study was to evaluate and compare the effectiveness of three cefpodoxime regimens against H. influenzae and S. pneumoniae isolates to determine if QD regimens provide activity similar to that of a conventional BID regimen. Our findings demonstrated that the BID regimens were associated with the greatest degree of activity against each study isolate. In experiments involving S. pneumoniae isolates, there appeared to be a greater likelihood of success associated with QD cefpodoxime administration (400 mg/day); however, further in vivo studies are necessary. The recent U.S. Food and Drug Administration approval of the QD cefpodoxime suspension for acute otitis media and ongoing trials evaluating other potential single-dose indications will provide valuable information regarding the potential use of cefpodoxime as a single-dose agent and its role relative to other orally available antimicrobial agents.

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REFERENCES


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