

## Comparison of Once-Daily versus Twice-Daily Administration of Cefdinir against Typical Bacterial Respiratory Tract Pathogens

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**In an in vitro pharmacodynamic model, a twice-daily cefdinir dosing regimen was more effective than a once-daily regimen against common bacterial respiratory pathogens in producing 3-log<sub>10</sub> killing and preventing the occurrence of regrowth at 24 h. Twice-daily administration is likely the more appropriate cefdinir dosing strategy for the treatment of community-acquired pneumonia.**

Cefdinir (Omnicef) is an oral extended-spectrum cephalosporin approved by the Food and Drug Administration for the treatment of several respiratory tract infections, including acute maxillary sinusitis, acute bacterial otitis media, acute exacerbations of chronic bronchitis, pharyngitis-tonsillitis, and community-acquired pneumonia. The drug has been shown to be effective against common respiratory pathogens including penicillin-susceptible strains of *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and  $\beta$ -lactamase-producing *Haemophilus influenzae* and *Moraxella catarrhalis* (Warner-Lambert Co. Omnicef (cefdinir) product information, August 1998). The recommended dose of cefdinir varies from 300 mg twice daily (BID) to 600 mg once daily (QD), depending on the type of infection, to be given for 10 days. Clinical trials with cefdinir have demonstrated that QD dosing is as effective as BID dosing against respiratory tract infections, excluding community-acquired pneumonia, in which QD dosing has not been studied (Warner-Lambert Co. Omnicef® (cefdinir) product information, August 1998). The purpose of this investigation was to determine whether a difference in the rate and extent of bacterial killing exists between QD and BID administration of cefdinir using an in vitro pharmacodynamic model. Such data would advocate appropriate dosing for obtaining maximal antibacterial activity with this cephalosporin in the treatment of community-acquired pneumonia and other respiratory tract infections.

A series of experiments were performed in a previously described in vitro pharmacodynamic model (8) using four clinical respiratory isolates—two strains of *S. pneumoniae*, a penicillin-susceptible strain (SP 30; penicillin MIC <0.06 mg/liter) and a non-penicillin-susceptible strain (S-53; penicillin MIC, 0.25 mg/liter), and two strains of *H. influenzae*, a  $\beta$ -lactamase-producing strain (HF 1746) and a non- $\beta$ -lactamase-producing strain (HF 2019). Each experiment was performed in duplicate for a duration of 24 h. The model consisted of a 290-ml sealed

glass chemostat, representing the central compartment, that was filled with either Todd-Hewitt broth with 0.5% yeast extract (Difco Laboratories, Detroit, Mich.) for *S. pneumoniae* or Haemophilus Test Medium (Becton Dickinson, Cockeysville, Md.) for *H. influenzae* and fitted with input and output tubing. Cefdinir was obtained from Parke-Davis (Morris Plains, N.J.) and prepared in accordance with the manufacturer's specifications, and stock solutions were stored at  $-80^{\circ}\text{C}$  until use. To simulate QD dosing in humans, an initial bolus of cefdinir was injected into the chemostat at time zero (achieving a peak concentration of 3 mg/liter), whereas for BID dosing, boluses were instilled at time zero and at h 12 (achieving a peak concentration of 1.6 mg/liter). Targeted concentrations were derived from reported data on human cefdinir pharmacokinetics. Although 60 to 70% of cefdinir is protein bound, we chose to simulate total serum concentrations in the model, as the significance of protein-binding values below 85 to 90% and the effect on tissue penetration and clinical impact are unclear (5). By pumping of antibiotic-free medium into the system at a rate of 1.7 ml/min with a peristaltic pump, an equal volume of antibiotic-containing medium was displaced. This resulted in the simulation of a monoexponential pharmacokinetic process that was adjusted to attain the desired cefdinir half-life of 2 h.

A suspension of each organism was allowed to grow overnight and diluted 1:10 in fresh medium prior to the experiment. The diluted suspension was reincubated for approximately 1 h to allow organisms to attain exponential growth. Upon comparison with a 0.5 McFarland equivalence turbidity standard (Remel, Lenexa, Kans.), an appropriate portion of the medium volume was added to the chemostat, producing an initial bacterial inoculum of  $10^6$  CFU/ml. The in vitro pharmacodynamic model was placed in a monitored  $37^{\circ}\text{C}$  water bath to maintain growth. Constant mixing of the microorganisms and antibiotic was ensured by placing a magnetic stirring bar in the bottom of each chamber. One-milliliter samples were taken at selected time intervals (baseline and 1, 2, 3, 5, 7, 12, 15, 18, 21, and 24 h) and plated onto either tryptic soy agar with 5% sheep blood (Remel) for *S. pneumoniae* or chocolate agar (Remel) for *H. influenzae*. Antibiotic carryover was prevented by saline dilution. Following incubation for 24 h at  $37^{\circ}\text{C}$  in 5 to 10%  $\text{CO}_2$ ,

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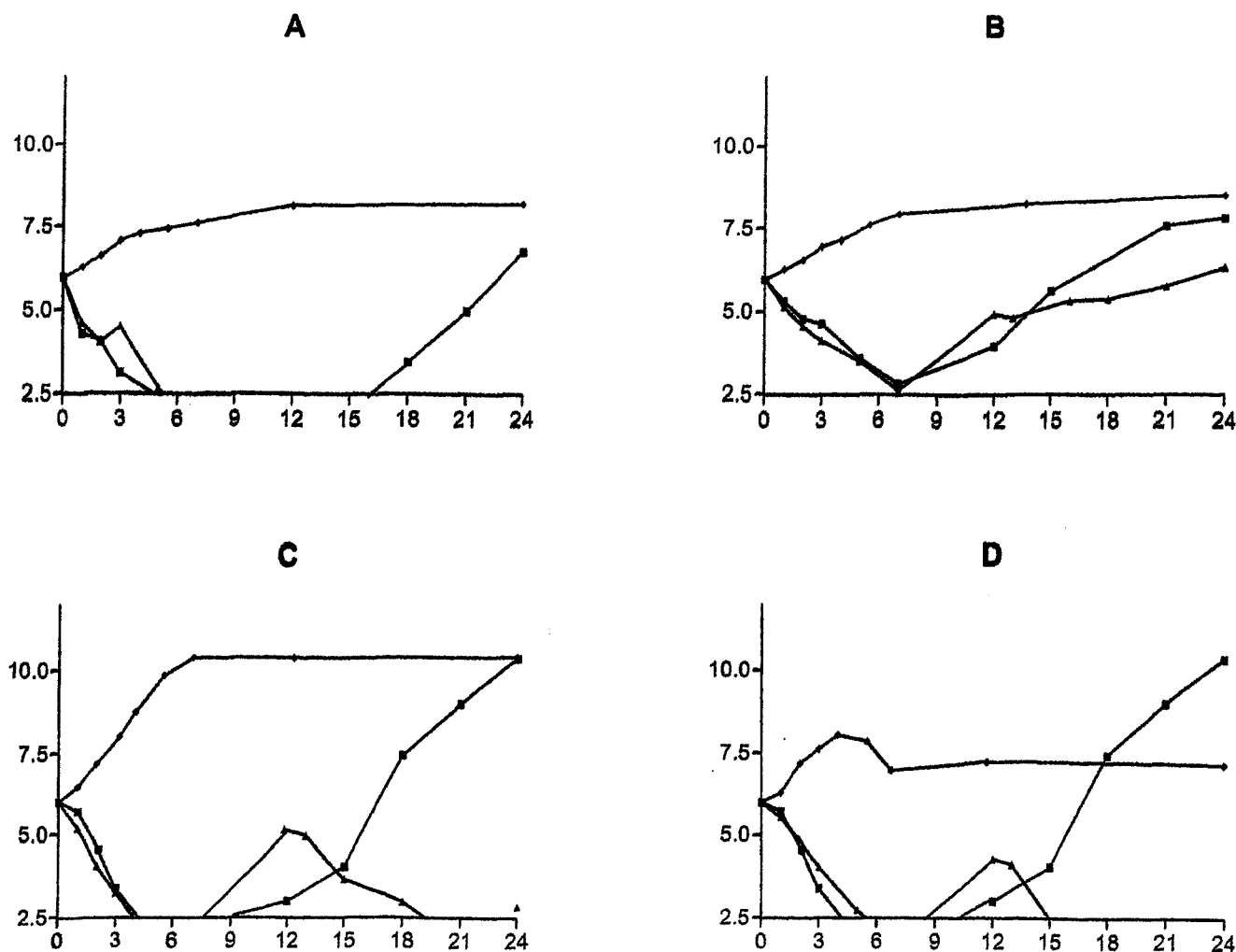


FIG. 1. Activity of cefdinir dose of 600 mg QD (■) and 300 mg BID (▲) against HF 1746 ( $\beta$ -lactamase-producing *H. influenzae*) (A), HF 2019 ( $\beta$ -lactamase negative *H. influenzae*) (B), SP 30 (penicillin-sensitive *S. pneumoniae*) (C), and S-53 (penicillin-intermediate *S. pneumoniae*) (D). Growth controls are represented by the symbol ◆.

agar plates containing 30 to 300 bacterial colonies were counted to construct the time-kill curves. The lower limit of bacterial detection in our laboratory has been determined to be  $3 \times 10^2$  CFU/ml.

The MIC of cefdinir for each organism was determined by broth microdilution techniques in accordance with NCCLS guidelines both prior to and after antibiotic exposure (4). An appropriate medium (Mueller-Hinton broth with 5% lysed horse blood [Becton Dickinson] for *S. pneumoniae* and Haemophilus Test Medium for *H. influenzae*) was used for all susceptibility testing. MICs were determined in quadruplicate by using an inoculum size of  $10^5$  to  $10^6$  CFU/ml and incubation without CO<sub>2</sub> for 16 to 20 h at 37°C. Quality control monitoring was done with *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922.

Evaluation of cefdinir concentrations was conducted by obtaining 1-ml samples at three separate time points over the 24-h period (1, 5, and 13 h). Cefdinir concentrations were verified by using an adapted microbiological assay using *Micrococcus luteus* ATCC 9341 as the indicator organism (6).

Briefly, blank 0.25-in. disks were spotted with 20  $\mu$ l of the standards or samples. We tested each standard in triplicate and each sample in duplicate by placing the disk onto previously prepared agar plates containing antibiotic medium no. 5 (Difco Laboratories) and *M. luteus*. Plates were incubated at 37°C for 24 to 28 h, after which the zone sizes were measured. Concentrations of 5.0, 2.5, 1.25, 0.625, and 0.3125 mg/liter were used as standards. The intraday coefficient of variation was <5% for each standard, while a correlation coefficient of  $\geq 0.98$  was achieved for all samples.

Quantitative bacterial cell counts were performed by using serial 10-fold dilutions and standard plate-counting techniques. Time-kill curves were analyzed for the rate and extent of bacterial killing. Time to 3-log killing (T3K) or time to 99.9% reduction of the initial inoculum size was determined by linear regression using GraphPad Prism 3.0 (GraphPad Software, Inc., San Diego, Calif.). Extent of bacterial killing was assessed by the presence or absence of regrowth at 24 h. The percentage of the dosing interval during which cefdinir concentrations remained above the MIC for the organism (T >

MIC), peak concentration to MIC, and area under the concentration-time curve to MIC were verified from drug concentration analysis and pre-run MIC data to evaluate the relationship between the pharmacodynamic parameter and the antibacterial effect (3). Peak concentration, minimum concentration, and half-life were calculated by standard noncompartmental pharmacokinetic equations (7).

The MICs of cefdinir for SP 30, S-53, HF 1746, and HF 2019 were 0.25, 0.5, 0.25, and 0.25 mg/liter, respectively, and are similar to those reported in the literature. All postexposure MICs were within 1 doubling tube dilution of pre-exposure MICs. No difference was found between the QD and BID dosing schemes in the initial rate of killing of either strain of *H. influenzae* (T3K, 3.2 and 4.4 h for HF 1746 and 6.5 and 6.2 h for HF 2019) or *S. pneumoniae* (T3K, 3.75 and 3.6 h for SP 30 and 4.5 and 4.7 h for S-53) (Fig. 1). Regrowth occurred with all isolates between 7 and 15 h after drug administration with the QD regimen and between 5 and 12 h with three of the four isolates after the first dose under the BID regimen. Regrowth at 24 h, however, was typically prevented by administering the second daily dose. The exception was HF 2019. Unexpectedly, regrowth of this  $\beta$ -lactamase-negative strain was apparent by 7 to 12 h and was sustained throughout the 24-h period despite repeated dosing at 12 h.

With the data accumulated from in vitro and animal infection models, the pharmacodynamic index that best correlates with a bacteriologic cure for  $\beta$ -lactams is  $T > MIC$  (1). Against *S. pneumoniae* and *H. influenzae*, a retrospective/pharmacodynamic analysis of double-tap specimens found that the times above the MIC required for at least a 90% bacteriologic cure in acute otitis media and acute maxillary sinusitis were generally 40 to 50% (2). Based on this breakpoint, with cefdinir MICs of 0.25 to 0.5 mg/liter for *H. influenzae* and *S. pneumoniae*,  $T > MIC$ s of only 22 to 30% are achieved with the QD regimen while  $T > MIC$ s of 28 to 45% are achieved with the BID regimen. As the initial rate of killing was unaffected by the dose employed and AUCs were virtually identical between dosing regimens (24-h AUC for the QD regimen, 8.66  $\mu\text{g} \cdot \text{h}/\text{ml}$ ; 24-h AUC for the BID regimen, 9.17  $\mu\text{g} \cdot \text{h}/\text{ml}$ ), the peak concentration to MIC and AUC to MIC were not indicative of antimicrobial efficacy.  $T > MIC$  also did not correlate with antimicrobial efficacy in our model. For example, a  $T > MIC$  of 28% was effective in producing 3-log killing and preventing regrowth of S-53 under the BID dosing regimen, whereas  $T >$

MICs of 30 and 45% were ineffective in preventing regrowth of HF 2019 with the BID regimen or that of HF 1746 with the QD regimen, respectively. Therefore, based on the presence of regrowth at 24 h alone, our results do not support the QD administration of cefdinir for the treatment of infections due to *S. pneumoniae* and *H. influenzae*. With in vitro data, however, we cannot determine whether 3-log killing is sufficient in lowering the bacterial burden to the point where the human immune system can rid the body of the infection. Accordingly, we are unsure how regrowth in the model correlates with efficacy, or lack thereof, in the clinical setting. Certainly, success with the QD dosing of cefdinir in clinical studies of upper respiratory tract infections has been achieved. Furthermore, as only a small number of isolates were included, this study may not take into account strain-to-strain variability. In conclusion, the BID cefdinir dosing regimen was effective against three of the four bacterial strains tested in producing a 99.9% decrease in the initial bacterial load and preventing the occurrence of regrowth at 24 h and is therefore likely the more appropriate cefdinir dosing strategy for the treatment of community-acquired pneumonia.

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