Antibacterial Activities of Cefpodoxime, Cefixime, and Ceftriaxone

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Cefpodoxime, cefixime, and ceftriaxone inhibited Branhamella catarrhalis at ≤1 μg/ml, beta-hemolytic streptococci at ≤0.25 μg/ml, Neisseria meningitidis at ≤0.06 μg/ml, and Haemophilus influenzae (other than β-lactamase-negative, ampicillin-resistant isolates) at ≤0.12 μg/ml. The MICs for 50% of isolates of the family Enterobacteriaceae other than Citrobacter freundii, Enterobacter aerogenes, and Enterobacter cloacae were ≤1 μg/ml for all three cephalosporins. The MICs of each cephalosporin for 90% of staphylococci, enterococci, and Pseudomonas aeruginosa isolates were >16 μg/ml. Inoculum effects were noted with cefpodoxime and cefixime with β-lactamase-positive H. influenzae.

Cefpodoxime proxetil (U-76,252; CS-807) is a new oral broad-spectrum cephalosporin ester which is de-esterified in the intestine to its active metabolite cefpodoxime (U-76,253; R-3763) (2, 6) and has been found to be active in vitro against streptococci, methicillin-susceptible staphylococci, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, indole-positive and -negative Proteus spp., Providencia rettgeri, Haemophilus influenzae, Neisseria spp., and Branhamella catarrhalis at concentrations of ≤4 μg/ml (3, 6). Cefpodoxime has also been shown to be stable to plasmid-mediated β-lactamases (3, 6).

The objective of this study was to compare the in vitro activities of the sodium salt of cefpodoxime (U-76,253A; R-3763) (hereafter referred to as cefpodoxime), cefixime, and ceftriaxone against a broad spectrum of nearly 1,400 clinical isolates of bacteria. All strains tested were either fresh or stock clinical isolates from specimens of patients at The Cleveland Clinic Foundation. An additional collection of 16 isogenic pairs of wild type and mutants of gram-negative bacilli derepressed for class I β-lactamase and 12 derepressed mutants without wild-type pairs (kindly provided by Christine C. Sanders, Creighton University, Omaha, Nebr.) were tested.

The sodium salt of cefpodoxime was provided by The Upjohn Co., Kalamazoo, Mich.; cefixime was provided by Lederle Laboratories, Pearl River, N.Y.; and ceftriaxone was provided by Roche Laboratories, Nutley, N.J. Each powder was constituted and stored according to the directions of the manufacturer.

MICs were determined with an inoculum of approximately 5 × 10^5 CFU/ml by the broth microdilution method and with controls recommended by the National Committee for Clinical Laboratory Standards (4). The determination of ≥99.9% bactericidal activity (MBC) was done by the procedure described by Shanholzer et al. (5), by subculturing 0.1 ml from each well without visible growth onto blood agar. The initial inoculum used for determination of the MBC for staphylococci was in the early- to mid-logarithmic phase of growth. Inocula of approximately 5 × 10^5 and 5 × 10^6 CFU of 10 isolates each of Staphylococcus aureus and H. influenzae per ml were used to determine inoculum effects on the activities of the cephalosporins tested.

The MICs of cefpodoxime, cefixime, and ceftriaxone are listed in Table 1. Cefpodoxime was inhibitory at concentrations of ≤1 μg/ml to 90% of isolates of B. catarrhalis, Citrobacter diversus, E. coli, Proteus mirabilis, Proteus vulgaris, and Providencia stuartii. Against these same species, the MICs of cefixime and ceftriaxone for 90% of isolates (MIC_{90}) were generally two- to fourfold lower than those of cefpodoxime. MIC_{90} were >16 μg/ml for cefpodoxime, cefixime, and ceftriaxone per ml for Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Pseudomonas aeruginosa, and Pseudomonas maltophilia, as well as for all mutants derepressed for type I β-lactamase. All three cephalosporins inhibited Neisseria meningitidis, beta-hemolytic streptococci, and Streptococcus pneumoniae at concentrations of ≤0.06 μg/ml. Both β-lactamase-positive and -negative isolates of H. influenzae were inhibited by ≤0.12 μg/ml of all three cephalosporins per ml; however, against two isolates of β-lactamase-negative, ampicillin-resistant H. influenzae, MICs were as follows: cefpodoxime, 1 and 2 μg/ml; cefixime, 0.25 and 1 μg/ml; and ceftriaxone, ≤0.06 μg/ml. Although MICs of cefpodoxime, cefixime, and ceftriaxone for 50% of methicillin-susceptible isolates (MIC_{50}) of S. aureus were 4, 16, and 4 μg/ml, respectively, the MIC_{90}s were all >16 μg/ml. None of the cephalosporins was active against methicillin-resistant staphylococci or enterococci.

MBC/MIC ratios were ≤4 for all cephalosporins against 9 isolates of S. aureus, 10 isolates of E. coli, 13 isolates of K. pneumoniae, and 20 other gram-negative isolates belonging to various species. The single exception was one isolate of E. coli for which the MBC/MIC ratio was 8.

There was a minimal effect on MICS (≤1 log, dilution) of each cephalosporin from increasing the inoculum of β-lactamase-negative S. aureus from 5 × 10^3 to 5 × 10^7 CFU/ml. With an increase in inoculum of non-β-lactamase-producing H. influenzae from 5 × 10^3 to 5 × 10^7 CFU/ml, the MICs of cefpodoxime and cefixime increased two to four times. With the higher inoculum of four β-lactamase-producing H. influenzae strains, the MICs of cefpodoxime and cefixime increased 2 to 8 and 16 to >256 times, respectively. There were no inoculum effects on the MICs of ceftriaxone by either β-lactamase-positive or -negative H. influenzae.

There were 14 MIC determinations for E. coli ATCC 25922, of which 2 were 0.12 μg and 12 were 0.25 μg of cefpodoxime per ml. Of 10 MIC determinations for S. aureus ATCC 29213, 4 were 2 μg and 6 were 4 μg of cefpodoxime.

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The MICs of cepodoxime, cefixime, and ceftriaxone for various bacteria are presented in Table 1. The MICs were determined in a range of 0.06 to 16 μg/ml. The table shows that cepodoxime had the widest range of activity, followed by cefixime and then ceftriaxone.

Our results confirm those of Utsui et al. (6), Jones and Barry (3), and Fass and Hesel (1) regarding the activity of cepodoxime against B. catarrhalis, H. influenzae, streptococci, and genera of the Enterobacteriaceae other than Citrobacter, Enterobacter, Serratia, and Morganella. Our data also confirm those of Utsui et al. (6) in demonstrating somewhat greater (two- to fourfold) activity of cefixime than of cepodoxime against members of the Enterobacteriaceae. In general, however, our MICs of cepodoxime and cefixime for C. freundii, E. aerogenes, and E. cloacae were substantially higher than those previously reported for these species (3, 6). Our MIC data more nearly resembled those reported by Fass and Hesel (1). Possible reasons for these discrepancies are (i) differences in the incidence in each study of mutants of members of the Enterobacteriaceae tested that were derepressed for class I β-lactamase and (ii) differences in inoculum sizes among the studies. Because of the marked inoculum effects on cephalosporin activity by β-lactamase-producing, gram-negative bacilli, testing with inocula below the 5 x 10^2 CFU/ml recommended by the National Committee for Clinical Laboratory standards (4) cannot be considered a true test of resistant isolates. For this reason, it is standard quality control procedure in our laboratory to monitor quantitatively on a regular basis the inoculum size used for susceptibility testing. Although Utsui et al. (6) and Jones and Barry (3) reported MICs of 1.56 and 4 μg/ml, respectively, for cepodoxime against methicillin-susceptible S. aureus, only 50% of our methicillin-susceptible strains were inhibited by 4 μg/ml, and 90% required 16 μg/ml for inhibition. Finally, we concur with the previous investigations as regards the bactericidal activity of cepodoxime against staphylococci and members of the Enterobacteriaceae and the marked inoculum effects on cepodoxime and cefixime by β-lactamase-producing, gram-negative bacilli. Our data with β-lactamase-producing isolates of H. influenzae demonstrated a marked difference in inoculum sensitivity between cepodoxime or cefixime and ceftriaxone. What implications this difference may have on the management of patients who are initially treated with a parenteral cephalosporin for a serious β-lactamase-producing H. influenzae infection and who are then considered for follow-up oral cephalosporin therapy remain to be seen.

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LITERATURE CITED


