

Antibacterial Activities of Cefpodoxime, Cefixime, and Ceftriaxone

CYNTHIA C. KNAPP, JUAN SIERRA-MADERO, AND JOHN A. WASHINGTON*

Department of Microbiology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195

Received 20 June 1988/Accepted 20 September 1988

Cefpodoxime, cefixime, and ceftriaxone inhibited *Branhamella catarrhalis* at ≤ 1 $\mu\text{g/ml}$, beta-hemolytic streptococci at ≤ 0.25 $\mu\text{g/ml}$, *Neisseria meningitidis* at ≤ 0.06 $\mu\text{g/ml}$, and *Haemophilus influenzae* (other than β -lactamase-negative, ampicillin-resistant isolates) at ≤ 0.12 $\mu\text{g/ml}$. The MICs for 50% of isolates of the family *Enterobacteriaceae* other than *Citrobacter freundii*, *Enterobacter aerogenes*, and *Enterobacter cloacae* were ≤ 1 $\mu\text{g/ml}$ for all three cephalosporins. The MICs of each cephalosporin for 90% of staphylococci, enterococci, and *Pseudomonas aeruginosa* isolates were > 16 $\mu\text{g/ml}$. 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 $\mu\text{g/ml}$ (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 $\geq 99.9\%$ bactericidal activity (MBC) was done by the procedure described by Shanholtzer 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 5×10^7 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 $\mu\text{g/ml}$ 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 (MIC₉₀s) were generally two- to fourfold lower than those of cefpodoxime. MIC₉₀s were > 16 μg of 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 $\mu\text{g/ml}$. Both β -lactamase-positive and -negative isolates of *H. influenzae* were inhibited by ≤ 0.12 μg 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 $\mu\text{g/ml}$; cefixime, 0.25 and 1 $\mu\text{g/ml}$; and ceftriaxone, ≤ 0.06 $\mu\text{g/ml}$. Although MICs of cefpodoxime, cefixime, and ceftriaxone for 50% of methicillin-susceptible isolates (MIC₅₀s) of *S. aureus* were 4, 16, and 4 $\mu\text{g/ml}$, respectively, the MIC₉₀s were all > 16 $\mu\text{g/ml}$. 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 log₂ dilution) of each cephalosporin from increasing the inoculum of β -lactamase-positive *S. aureus* from 5×10^5 to 5×10^7 CFU/ml. With an increase in inoculum of non- β -lactamase-producing *H. influenzae* from 5×10^5 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

* Corresponding author.

TABLE 1. Comparative activities of cefpodoxime, cefixime, and ceftriaxone

Organism(s) (no. of isolates tested)	MIC ($\mu\text{g/ml}$)								
	Cefpodoxime			Cefixime			Ceftriaxone		
	Range	50%	90%	Range	50%	90%	Range	50%	90%
<i>Acinetobacter anitratus</i> (21)	2-16	8	8	2-16	4	8	2-16	8	8
<i>Branhamella catarrhalis</i> (17)	≤ 0.06 -1	0.5	1	≤ 0.06 -0.25	0.25	0.25	≤ 0.06 -0.5	0.125	0.5
<i>Neisseria meningitidis</i> (10)	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
<i>Haemophilus influenzae</i> (13)	≤ 0.06 -2	≤ 0.06	≤ 0.12	≤ 0.06 -1	≤ 0.06	≤ 0.06	≤ 0.06 -0.12	≤ 0.06	0.12
<i>Citrobacter diversus</i> (15)	0.12-1	0.25	1	≤ 0.06 -0.25	≤ 0.06	0.12	≤ 0.06	≤ 0.06	≤ 0.06
<i>Citrobacter freundii</i> (31)	0.5->16	2	>16	0.25->16	2	>16	≤ 0.06 ->16	≤ 0.06	>16
<i>Enterobacter aerogenes</i> (32)	≤ 0.06 ->16	4	>16	≤ 0.06 ->16	16	>16	≤ 0.06 ->16	2	>16
<i>Enterobacter cloacae</i> (47)	≤ 0.06 ->16	>16	>16	≤ 0.06 ->16	>16	>16	≤ 0.06 ->16	4	>16
<i>Escherichia coli</i> (305)	≤ 0.06 -16	0.25	0.5	≤ 0.06 -16	0.12	0.5	≤ 0.06 -8	≤ 0.06	≤ 0.06
<i>Klebsiella oxytoca</i> (31)	≤ 0.06 -1	≤ 0.06	0.25	≤ 0.06 -0.12	≤ 0.06	≤ 0.06	≤ 0.06 -2	≤ 0.06	≤ 0.06
<i>Klebsiella pneumoniae</i> (97)	≤ 0.06 ->16	0.12	8	≤ 0.06 -2	≤ 0.06	0.5	≤ 0.06 ->16	≤ 0.06	2
<i>Morganella morganii</i> (23)	0.12->16	8	>16	≤ 0.06 ->16	2	>16	≤ 0.06 -4	≤ 0.06	2
<i>Proteus mirabilis</i> (87)	≤ 0.06 ->16	≤ 0.06	0.12	≤ 0.06 ->16	≤ 0.06	≤ 0.06	≤ 0.06 -2	≤ 0.06	≤ 0.06
<i>Proteus vulgaris</i> (12)	≤ 0.06 -1	0.12	0.25	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
<i>Providencia rettgeri</i> (10)	≤ 0.06 -8	0.5	1	≤ 0.06 -4	0.25	2	≤ 0.06 -8	0.12	4
<i>Providencia stuartii</i> (10)	≤ 0.06 -2	0.12	0.5	≤ 0.06 -4	≤ 0.06	0.5	≤ 0.06 -0.25	≤ 0.06	0.25
<i>Serratia marcescens</i> (27)	0.12->16	1	8	≤ 0.06 ->16	0.25	2	≤ 0.06 ->16	0.12	0.5
<i>Pseudomonas aeruginosa</i> (212)	0.5->16	>16	>16	0.25->16	>16	>16	≤ 0.06 ->16	8	>16
<i>Pseudomonas cepacia</i> (11)	1->16	4	16	0.5->16	1	2	0.5->16	2	16
<i>Pseudomonas maltophilia</i> (26)	>16	>16	>16	16->16	>16	>16	8->16	>16	>16
<i>Staphylococcus aureus</i> , methicillin susceptible (67)	2->16	4	>16	4->16	16	>16	2->16	4	>16
<i>Staphylococcus aureus</i> , methicillin resistant (21)	4->16	>16	>16	16->16	>16	>16	4->16	>16	>16
Staphylococci, coagulase negative (41)	≤ 0.06 ->16	2	>16	≤ 0.06 ->16	8	>16	≤ 0.06 ->16	2	>16
Streptococci, beta-hemolytic (42)	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06 -0.25	≤ 0.06	0.25	≤ 0.06	≤ 0.06	≤ 0.06
Enterococci (46)	0.12->16	>16	>16	2->16	>16	>16	≤ 0.06 ->16	>16	>16
<i>Streptococcus pneumoniae</i> (15)	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06 -0.12	≤ 0.06	0.12	≤ 0.06	≤ 0.06	≤ 0.06

per ml. The MICs of cefpodoxime for *P. aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212 were >16 $\mu\text{g/ml}$. The MICs of cefixime were 16 $\mu\text{g/ml}$ for *S. aureus* ATCC 29213 and ≤ 0.06 to 0.25 $\mu\text{g/ml}$ for *E. coli* ATCC 25922. The MICs of ceftriaxone for the reference strains were within acceptable ranges listed by the National Committee for Clinical Laboratory Standards (4).

Our results confirm those of Utsui et al. (6), Jones and Barry (3), and Fass and Helsel (1) regarding the activity of cefpodoxime 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 cefpodoxime against members of the *Enterobacteriaceae*. In general, however, our MIC₅₀s of cefpodoxime 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 Helsel (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 5×10^5 CFU/ml recommended by the National Committee for Clinical Laboratory Standards (4) could decrease detection of resistant isolates. For this reason, it is standard quality control procedure in our laboratory to monitor quantitatively on a regular basis the inocu-

lum size used for susceptibility testing. Although Utsui et al. (6) and Jones and Barry (3) reported MIC₉₀s of 1.56 and 4 $\mu\text{g/ml}$, respectively, for cefpodoxime against methicillin-susceptible *S. aureus*, only 50% of our methicillin-susceptible strains were inhibited by 4 $\mu\text{g/ml}$, and 90% required >16 $\mu\text{g/ml}$ for inhibition. Finally, we concur with the previous investigations as regards the bactericidal activity of cefpodoxime against staphylococci and members of the *Enterobacteriaceae* and the marked inoculum effects on cefpodoxime 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 cefpodoxime 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.

We thank Lynne Atkinson for medium preparation and Estella Stovall for manuscript preparation.

We are grateful to The Upjohn Co. for financial support of this project.

LITERATURE CITED

- Fass, R. J., and V. L. Helsel. 1988. In vitro activity of U-76,252 (CS-807), a new oral cephalosporin. *Antimicrob. Agents Chemother.* 32:1082-1085.
- Fujimoto, K., S. Ishihara, H. Yanagisawa, J. Ide, E. Nakayama, H. Nakao, S. Sugawara, and M. Iwata. 1987. Studies on orally active cephalosporin esters. *J. Antibiot.* 40:370-384.
- Jones, R. N., and A. L. Barry. 1988. Antimicrobial activity and

- disk diffusion susceptibility testing of U-76,253A (R-3746), the active metabolite of the new cephalosporin ester, U-76,252 (CS-807). *Antimicrob. Agents Chemother.* **32**:443–449.
4. **National Committee for Clinical Laboratory Standards.** 1985. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard M7A. National Committee for Clinical Laboratory Standards, Villanova, Pa.
 5. **Shanholtzer, C. J., L. R. Peterson, M. L. Mohn, J. A. Moody, and D. N. Gerding.** 1984. MBCs for *Staphylococcus aureus* as determined by macrodilution and microdilution techniques. *Antimicrob. Agents Chemother.* **26**:214–219.
 6. **Utsui, Y., M. Inoue, and S. Mitsuhashi.** 1987. In vitro and in vivo antibacterial activities of CS-807, a new oral cephalosporin. *Antimicrob. Agents Chemother.* **31**:1085–1092.