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Activity of CP 99,219 Compared with Those of Ciprofloxacin, Grepafloxacin, Metronidazole, Cefoxitin, Piperacillin, and Piperacillin-Tazobactam against 489 Anaerobes

S. K. SPANGLER,[1] M. R. JACOBS,[2] AND P. C. APPELBAUM[1]*

Department of Pathology (Clinical Microbiology), Hershey Medical Center, Hershey, Pennsylvania 17033,[1] and Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106[2]

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Agar dilution was used to compare the in vitro activity of CP 99,219 with those of ciprofloxacin, grepafloxacin, metronidazole, cefoxitin, piperacillin, and piperacillin-tazobactam against 489 anaerobes. CP 99,219 yielded a MIC for 50% of the strains tested (MIC_{50}) of 0.25 μg/ml and a MIC_{90} of 1.0 μg/ml, with 99.6% of the strains susceptible at a breakpoint of 2.0 μg/ml. Ciprofloxacin and grepafloxacin were less active (MIC_{50}, 4.0 μg/ml; MIC_{90}, 32.0 μg/ml and 2.0 and 16.0 μg/ml, respectively). Metronidazole was active against all gram-negative rods (MIC_{90}, 4.0 μg/ml), but 31% of the gram-positive anaerobes were resistant at >8.0 μg/ml. Cefoxitin was active against 84% of all strains at ≤16.0 μg/ml, with a MIC_{50} of 4.0 μg/ml and a MIC_{90} of 32.0 μg/ml. Tazobactam enhanced the activity of piperacillin against >95% of the β-lactamase-producing gram-negative anaerobic rods (MIC_{90}, 16.0 μg/ml).

Anaerobes are becoming increasingly resistant to β-lactams because of β-lactamase production and other mechanisms. Metronidazole resistance in organisms other than non-spore-forming gram-positive rods has been described previously, as has clindamycin resistance in anaerobic gram-negative rods (1–5).

Commercially available quinolones, such as ciprofloxacin, ofloxacin, fleroxacin, pefloxacin, enoxacin, and lomefloxacin, are inactive or marginally active against anaerobes, with MICs either higher than or clustering around breakpoints. Experimental quinolones with increased anti-anaerobic activity include (i) those with slightly increased activity (sparfloxacin, OPC 17116 [grepafloxacin], tosufloxacin, temafloxacin [now discontinued], CI-990, AM-1155, and levofloxacin) and (ii) those with significantly improved anti-anaerobic activity (Win 57273, Bay y3118, clinafloxacin, and DU-6859a) (6–8, 12, 19, 24, 25). Development of both Win 57273 and Bay y3118 has been discontinued because of toxicity.

CP 99,219 is a novel investigational trifluoronaphthyridone with a structure differing from those of norfloxacin, ciprofloxacin, and enoxacin. It contains the C-7 moiety 7-(3-azabicyclo [3.1.0.]hexyl) on a basic naphthyridone configuration (9). The bicyclo C-7 substitution has been previously evaluated and described for CP-74,667 (17). The 1-*N* substitution of CP 99,219 is a difluorinated structure identical to that of tosufloxacin that produces enhanced activity against some ciprofloxacin-resistant strains. CP 99,219 possesses a broad spectrum of activity against gram-positive and -negative organisms, including those resistant to ciprofloxacin (9, 10, 13, 14, 18, 21). This study uses standardized agar dilution techniques to examine the susceptibilities of 489 recently isolated clinical anaerobes to CP 99,219 compared with those of ciprofloxacin, grepafloxacin, metronidazole, cefoxitin, piperacillin, and piperacillin-tazobactam.

Anaerobes were clinical isolates collected between 1989 and 1994 that were identified by standard procedures (15, 22) and kept frozen in double-strength skim milk at −70°C until use. Gram-negative strains were selected for their β-lactamase production, but gram-positive organisms were not selected and were consecutive isolates. Approximately 20% of all strains were tested in previous studies (1–5), but 80% were fresh clinical strains isolated within the past 2 years. Nonselected fresh fusobacterial strains were kindly provided by J. Rosenblatt (Mayo Clinic, Rochester, Minn.) to augment our collection, which had become depleted because of a lack of viability after thawing. Prior to testing, strains were subcultured twice onto enriched sheep blood agar plates (1). Strains were tested for purity by Gram staining and colonial morphology.

Susceptibility powders of known potency were obtained from the following suppliers: CP 99,219, Pfizer Central Research, Groton, Conn.; ciprofloxacin, Miles, Inc., West Haven, Conn.; grepafloxacin, Otsuka Laboratories, Rockville, Md; metronidazole, Searle Laboratories, Skokie, Ill.; cefoxitin, Merck Research Laboratories, Rahway, N.J.; and piperacillin and tazobactam, Lederle Laboratories, Pearl River, N.Y. β-Lactamase testing was performed by the nitrocefin disk method (Cefinase; BBL Microbiology Systems, Cockeysville, Md.) (4). Agar dilution susceptibility testing was performed according to the method recommended by the National Committee for Clinical Laboratory Standards (20) with Wilkins-Chalgren agar, supplemented with 5% sterile defibrinated sheep blood for non-*Bacteroides fragilis* group strains. Tazobactam was added to piperacillin at a fixed concentration of 4.0 μg/ml.

The following dilution ranges were used: CP 99,219, grepafloxacin, ciprofloxacin, cefoxitin, and piperacillin-tazobactam, 0.016 to 64.0 μg/ml; metronidazole, 0.016 to 16.0 μg/ml; and piperacillin, 0.016 to 256.0 μg/ml. The following breakpoints were used: CP 99,219, ciprofloxacin, and grepafloxacin, 0.5, 1.0, and 2.0 μg/ml, respectively; metronidazole, 8.0 and 16.0 μg/ml; cefoxitin, 16.0 and 32.0 μg/ml; and piperacillin and piperacillin-tazobactam, 32.0 and 64.0 μg/ml. Of all of the breakpoints described above, anaerobe breakpoints (as used in this study) are available from the National Committee for Clinical Laboratory Standards only for metronidazole (8.0 μg/ml), cefoxitin (16.0 μg/ml), and piperacillin with or without tazobactam (32.0

* Corresponding author. Mailing address: Department of Pathology, Hershey Medical Center, P.O. Box 850, Hershey, PA 17033. Phone: (717) 531-5113. Fax: (717) 531-5021.

TABLE 1. Antimicrobial susceptibility of anaerobic strains

Organism and agent	MIC (μg/ml)[a]			% Susceptibility[b]
	Range	50%	90%	
Bacteroides fragilis (63/63)[c]				
CP 99,219	0.06–1.0	0.125	0.5	97, 100, 100
Grepafloxacin	0.5–32.0	2.0	8.0	2, 3, 46
Ciprofloxacin	0.25–64.0	8.0	16.0	2, 2, 8
Metronidazole	0.25–4.0	1.0	4.0	100, 100
Cefoxitin	4.0–>64.0	16.0	>64.0	75, 79
Piperacillin	0.5–>256.0	16.0	>256.0	57, 73
Piperacillin-tazobactam	0.06–128.0	1.0	16.0	92, 92
Bacteroides thetaiotaomicron (31/31)				
CP 99,219	0.06–2.0	0.25	0.5	90, 97, 100
Grepafloxacin	0.5–32.0	2.0	8.0	26, 39, 61
Ciprofloxacin	2.0–64.0	4.0	32.0	19, 29, 48
Metronidazole	0.06–4.0	1.0	2.0	100, 100
Cefoxitin	4.0–32.0	8.0	64.0	77, 87
Piperacillin	0.25–>256.0	16.0	>256.0	81, 81
Piperacillin-tazobactam	0.06–64.0	1.0	8.0	100, 100
Bacteroides ovatus (18/18)				
CP 99,219	0.06–2.0	0.25	1.0	83, 94, 100
Grepafloxacin	0.5–32.0	4.0	16.0	6, 22, 22
Ciprofloxacin	2.0–64.0	8.0	64.0	0, 0, 11
Metronidazole	0.06–4.0	2.0	2.0	100, 100
Cefoxitin	4.0–>64.0	16.0	>64.0	72, 89
Piperacillin	0.25–128.0	32.0	>256.0	61, 72
Piperacillin-tazobactam	0.06–64.0	1.0	16.0	100, 100
Bacteroides distasonis (26/26)				
CP 99,219	0.03–1.0	0.5	1.0	88, 100, 100
Grepafloxacin	0.25–32.0	4.0	16.0	8, 12, 31
Ciprofloxacin	0.5–64.0	8.0	32.0	4, 12, 15
Metronidazole	0.125–4.0	1.0	2.0	100, 100
Cefoxitin	1.0–64.0	8.0	64.0	73, 88
Piperacillin	0.5–>256.0	64.0	>256.0	42, 62
Piperacillin-tazobactam	0.06–128.0	8.0	32.0	96, 96
Bacteroides vulgatus (10/10)				
CP 99,219	0.06–0.5	0.25	0.5	60, 100, 100
Grepafloxacin	0.5–8.0	8.0	8.0	10, 10, 10
Ciprofloxacin	0.5–64.0	8.0	32.0	10, 20, 20
Metronidazole	0.5–2.0	1.0	2.0	100, 100
Cefoxitin	1.0–32.0	16.0	32.0	80, 100
Piperacillin	0.5–128.0	32.0	128.0	50, 80
Piperacillin-tazobactam	0.06–32.0	2.0	16.0	100, 100
Miscellaneous *B. fragilis* group (10/10)[d]				
CP 99,219	0.06–2.0	0.5	1.0	70, 90, 100
Grepafloxacin	0.25–16.0	4.0	16.0	10, 10, 30
Ciprofloxacin	0.25–64.0	8.0	64.0	10, 10, 10
Metronidazole	0.5–4.0	1.0	4.0	100, 100
Cefoxitin	0.25–>64.0	16.0	32.0	70, 90
Piperacillin	0.5–>256.0	32.0	256.0	50, 60
Piperacillin-tazobactam	0.06–16.0	2.0	8.0	100, 100
All *B. fragilis* group (158/158)				
CP 99,219	0.03–2.0	0.25	0.5	91, 98, 100
Grepafloxacin	0.125–32.0	4.0	8.0	9, 15, 41
Ciprofloxacin	0.125–>64.0	8.0	32.0	6, 10, 18
Metronidazole	0.06–4.0	1.0	2.0	100, 100
Cefoxitin	0.25–>64.0	16.0	>64.0	75, 85
Piperacillin	0.25–>256.0	32.0	>256.0	59, 72
Piperacillin-tazobactam	0.06–128.0	2.0	16.0	96, 96
Prevotella bivia (50/51)				
CP 99,219	0.06–4.0	1.0	1.0	39, 90, 98
Grepafloxacin	0.125–64.0	16.0	16.0	2, 4, 14
Ciprofloxacin	0.25–64.0	32.0	32.0	2, 2, 4

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TABLE 1—*Continued*

Organism and agent	MIC (μg/ml)[a]			% Susceptibility[b]
	Range	50%	90%	
Metronidazole	0.25–8.0	2.0	4.0	100, 100
Cefoxitin	0.125–32.0	1.0	16.0	92, 100
Piperacillin	0.06–256.0	16.0	64.0	80, 96
Piperacillin-tazobactam	0.06–32.0	0.06	8.0	100, 100
Prevotella disiens (9/10)				
CP 99,219	0.25–1.0	0.5	1.0	80, 100, 100
Grepafloxacin	1.0–2.0	2.0	2.0	0, 20, 100
Ciprofloxacin	2.0–8.0	4.0	4.0	0, 0, 20
Metronidazole	1.0–4.0	2.0	4.0	100, 100
Cefoxitin	0.25–4.0	0.5	2.0	100, 100
Piperacillin	0.5–64.0	8.0	32.0	90, 100
Piperacillin-tazobactam	0.06–0.25	0.06	0.06	100, 100
Prevotella oralis (16/16)				
CP 99,219	0.03–1.0	0.5	1.0	75, 100, 100
Grepafloxacin	0.25–32.0	8.0	32.0	6, 25, 31
Ciprofloxacin	0.5–32.0	16.0	32.0	6, 6, 6
Metronidazole	1.0–4.0	1.0	4.0	100, 100
Cefoxitin	0.25–32.0	2.0	16.0	94, 100
Piperacillin	2.0–256.0	32.0	256.0	50, 81
Piperacillin-tazobactam	0.06–32.0	0.06	16.0	100, 100
Prevotella melaninogenica (9/11)				
CP 99,219	0.03–1.0	0.25	1.0	73, 100, 100
Grepafloxacin	0.125–32.0	1.0	16.0	36, 73, 73
Ciprofloxacin	0.125–32.0	4.0	16.0	18, 27, 45
Metronidazole	0.25–4.0	2.0	4.0	100, 100
Cefoxitin	0.25–16.0	2.0	16.0	100, 100
Piperacillin	0.06–128.0	16.0	64.0	82, 91
Piperacillin-tazobactam	0.06–16.0	0.06	8.0	100, 100
Prevotella intermedia (13/14)				
CP 99,219	0.06–1.0	0.5	1.0	43, 79, 100
Grepafloxacin	0.5–8.0	4.0	8.0	7, 21, 36
Ciprofloxacin	1.0–32.0	4.0	16.0	0, 14, 36
Metronidazole	0.25–8.0	1.0	4.0	100, 100
Cefoxitin	0.25–32.0	2.0	32.0	86, 100
Piperacillin	0.03–256.0	8.0	64.0	79, 93
Piperacillin-tazobactam	0.03–32.0	0.06	32.0	100, 100
Miscellaneous non-*B. fragilis* group and *Prevotella* spp. (15/15)[e]				
CP 99,219	0.06–1.0	0.25	1.0	80, 100, 100
Grepafloxacin	0.5–32.0	4.0	16.0	7, 20, 40
Ciprofloxacin	0.5–64.0	4.0	64.0	7, 13, 27
Metronidazole	0.5–4.0	2.0	4.0	100, 100
Cefoxitin	0.25–64.0	4.0	64.0	87, 87
Piperacillin	2.0–128.0	8.0	32.0	93, 93
Piperacillin-tazobactam	0.06–2.0	0.25	2.0	100, 100
All non-*B. fragilis* group *Bacteroides* and *Prevotella* spp. (112/117)				
CP 99,219	0.03–4.0	0.5	1.0	60, 96, 99
Grepafloxacin	0.125–64.0	4.0	16.0	8, 21, 37
Ciprofloxacin	0.25–64.0	8.0	32.0	4, 9, 18
Metronidazole	0.25–8.0	2.0	4.0	100, 100
Cefoxitin	0.125–64.0	1.0	16.0	93, 99
Piperacillin	0.03–256.0	16.0	64.0	79, 93
Piperacillin-tazobactam	0.03–32.0	0.06	8.0	100, 100
Fusobacterium nucleatum (3/11)				
CP 99,219	0.03–0.5	0.125	0.25	100, 100, 100
Grepafloxacin	0.125–2.0	0.5	2.0	64, 82, 100
Ciprofloxacin	0.125–4.0	0.5	4.0	64, 73, 73
Metronidazole	0.125–4.0	0.5	2.0	100, 100
Cefoxitin	0.25–4.0	1.0	2.0	100, 100

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TABLE 1—*Continued*

Organism and agent	MIC (μg/ml)[a]			% Susceptibility[b]
	Range	50%	90%	
Piperacillin	0.06–4.0	0.5	4.0	100, 100
Piperacillin-tazobactam	0.06–4.0	0.06	2.0	100, 100
Fusobacterium necrophorum (1/14)				
CP 99,219	0.03–1.0	0.125	0.5	93, 100, 100
Grepafloxacin	0.125–2.0	1.0	2.0	29, 86, 100
Ciprofloxacin	0.125–4.0	1.0	4.0	29, 64, 71
Metronidazole	0.125–2.0	1.0	2.0	100, 100
Cefoxitin	0.25–4.0	2.0	4.0	100, 100
Piperacillin	0.06–32.0	0.5	8.0	100, 100
Piperacillin-tazobactam	0.06–8.0	0.25	2.0	100, 100
Fusobacterium varium (3/11)				
CP 99,219	0.03–2.0	0.25	1.0	82, 91, 100
Grepafloxacin	0.125–64.0	4.0	16.0	9, 18, 45
Ciprofloxacin	0.125–64.0	8.0	32.0	9, 9, 18
Metronidazole	0.125–4.0	1.0	2.0	100, 100
Cefoxitin	0.25–32.0	4.0	16.0	91, 100
Piperacillin	0.06–64.0	4.0	8.0	91, 100
Piperacillin-tazobactam	0.06–2.0	0.5	2.0	91, 100
Miscellaneous fusobacteria (5/10)[f]				
CP 99,219	0.125–1.0	0.25	1.0	60, 100, 100
Grepafloxacin	0.5–2.0	1.0	2.0	20, 60, 100
Ciprofloxacin	1.0–2.0	2.0	2.0	0, 20, 100
Metronidazole	0.125–4.0	1.0	4.0	100, 100
Cefoxitin	0.125–16.0	2.0	8.0	100, 100
Piperacillin	2.0–32.0	8.0	32.0	100, 100
Piperacillin-tazobactam	0.5–16.0	1.0	8.0	100, 100
All fusobacteria (12/46)				
CP 99,219	0.03–2.0	0.25	1.0	87, 98, 100
Grepafloxacin	0.125–64.0	1.0	4.0	28, 61, 85
Ciprofloxacin	0.125–64.0	2.0	8.0	26, 43, 63
Metronidazole	0.125–4.0	1.0	2.0	100, 100
Cefoxitin	0.25–32.0	2.0	8.0	98, 100
Piperacillin	0.06–64.0	2.0	16.0	98, 100
Piperacillin-tazobactam	0.06–64.0	0.5	4.0	98, 100
Peptostreptococci (0/63)[g]				
CP 99,219	0.03–0.5	0.06	0.25	100, 100, 100
Grepafloxacin	0.125–8.0	1.0	2.0	37, 75, 95
Ciprofloxacin	0.125–8.0	1.0	4.0	44, 63, 86
Metronidazole	0.125–>16.0	2.0	>16.0	81, 84
Cefoxitin	0.25–>64.0	0.5	8.0	97, 97
Piperacillin	0.06–8.0	0.06	2.0	100, 100
Piperacillin-tazobactam	0.06–8.0	0.06	1.0	100, 100
Propionibacterium acnes (0/13)				
CP 99,219	0.06–1.0	0.25	0.5	92, 100, 100
Grepafloxacin	0.5–8.0	1.0	4.0	8, 54, 77
Ciprofloxacin	0.125–16.0	1.0	4.0	46, 62, 77
Metronidazole	1.0–>16.0	>16.0	>16.0	46, 46
Cefoxitin	0.25–16.0	0.25	16.0	100, 100
Piperacillin	0.06–2.0	0.5	1.0	100, 100
Piperacillin-tazobactam	0.06–1.0	0.5	1.0	100, 100
Miscellaneous gram-positive non-spore-forming rods (0/37)[h]				
CP 99,219	0.03–4.0	0.25	1.0	78, 89, 97
Grepafloxacin	0.125–32.0	1.0	16.0	35, 54, 62
Ciprofloxacin	0.125–64.0	2.0	64.0	22, 46, 59
Metronidazole	0.5–>16.0	>16.0	>16.0	30, 35
Cefoxitin	0.25–>64.0	16.0	64.0	59, 65
Piperacillin	0.06–16.0	0.5	8.0	100, 100
Piperacillin-tazobactam	0.06–8.0	0.25	4.0	100, 100

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TABLE 1—*Continued*

Organism and agent	MIC (μg/ml)[a]			% Susceptibility[b]
	Range	50%	90%	
Clostridium perfringens (0/20)				
CP 99,219	0.03–0.25	0.03	0.25	100, 100, 100
Grepafloxacin	0.125–8.0	0.5	1.0	65, 90, 95
Ciprofloxacin	0.125–2.0	0.125	0.5	90, 95, 100
Metronidazole	0.125–8.0	2.0	4.0	100, 100
Cefoxitin	0.25–2.0	0.25	1.0	100, 100
Piperacillin	0.06–1.0	0.06	0.06	100, 100
Piperacillin-tazobactam	0.06–1.0	0.06	0.06	100, 100
Clostridium difficile (0/12)				
CP 99,219	0.125–1.0	0.5	1.0	75, 100, 100
Grepafloxacin	2.0–32.0	8.0	32.0	0, 0, 17
Ciprofloxacin	2.0–32.0	8.0	32.0	0, 0, 33
Metronidazole	1.0–>16.0	2.0	8.0	92, 92
Cefoxitin	1.0–>64.0	32.0	>64.0	42, 50
Piperacillin	0.06–32.0	2.0	8.0	100, 100
Piperacillin-tazobactam	0.06–32.0	2.0	8.0	100, 100
Miscellaneous clostridia (1/23)[i]				
CP 99,219	0.03–0.5	0.125	0.5	100, 100, 100
Grepafloxacin	0.125–16.0	2.0	16.0	30, 48, 78
Ciprofloxacin	0.125–64.0	2.0	4.0	26, 48, 74
Metronidazole	0.125–>16.0	2.0	>16.0	74, 83
Cefoxitin	0.25–>64.0	2.0	>64.0	78, 78
Piperacillin	0.06–32.0	1.0	8.0	100, 100
Piperacillin-tazobactam	0.06–16.0	0.5	8.0	100, 100
All organisms (283/489)				
CP 99,219	0.03–4.0	0.25	1.0	84, 97, 99
Grepafloxacin	0.125–64.0	2.0	16.0	19, 37, 57
Ciprofloxacin	0.125–>64.0	4.0	32.0	19, 28, 42
Metronidazole	0.06–>16.0	2.0	8.0	90, 91
Cefoxitin	0.25–>64.0	4.0	32.0	84, 90
Piperacillin	0.03–>256.0	4.0	128.0	81, 89
Piperacillin-tazobactam	0.03–128.0	0.25	8.0	98, 99

[a] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

[b] For CP 99,219, grepafloxacin, and ciprofloxacin, values reflect the percentages susceptible at breakpoints of 0.5, 1.0, and 2.0 μg/ml, respectively. The following are the breakpoints for the other compounds: metronidazole, 8.0 and 16.0 μg/ml; cefoxitin, 16.0 and 32.0 μg/ml; piperacillin with or without tazobactam, 32.0 and 64.0 μg/ml.

[c] Number of β-lactamase-positive (nitrocefin disk test) species/total number tested.

[d] Nine *Bacteroides uniformis* and one *Bacteroides eggerthii*.

[e] Five *Bacteroides capillosus*, seven *Bacteroides ureolyticus*, two *Prevotella buccae*, one *Prevotella loeschei*.

[f] Nine *Fusobacterium mortiferum*, one *Fusobacterium gonidiaformans*.

[g] Fifteen *Peptostreptococcus asaccharolyticus*, 16 *Peptostreptococcus magnus*, 3 *Peptostreptococcus micros*, 11 *Peptostreptococcus anaerobius*, 14 *Peptostreptococcus tetradius*, 1 *Peptostreptococcus hydrogenalis*, 1 *Peptostreptococcus* species, 2 *Streptococcus intermedius*.

[h] Five *Eubacterium lentum*, seven *Lactobacillus acidophilus*, four *Lactobacillus casei*, one *Lactobacillus fermentum*, one *Lactobacillus plantarum*, five *Lactobacillus* spp., two *Bifidobacterium breve*, four *Bifidobacterium* spp., four *Actinomyces naeslundii*, two *Actinomyces meyeri*, one *Actinomyces odontolyticus*, one *Actinomyces viscosus*.

[i] One *Clostridium ramosum*, one *Clostridium fallax*, one *Clostridium subterminale*, six *Clostridium tertium*, seven *Clostridium clostridioforme*, one *Clostridium sporogenes*, one *Clostridium cadaveris*, two *Clostridium sordellii*, two *Clostridium septicum*, one *Clostridium histolyticum*.

μg/ml) (20). Breakpoints for the other compounds tested are not currently provided by the National Committee for Clinical Laboratory Standards for anaerobes.

The results of susceptibility testing are presented in Table 1. As can be seen, all members of the *B. fragilis* group, 112 of 117 (95.7%) members of non-*B. fragilis* group *Bacteroides* and *Prevotella* species, and 12 of 46 (26.1%) members of the fusobacteria produced β-lactamase according to the nitrocefin disk method. By contrast, among gram-positive organisms, only one strain of *Clostridium clostridiiforme* (5) produced this enzyme.

CP 99,219 yielded an overall MIC for 50% of the strains tested (MIC_{50}) of 0.25 μg/ml and a MIC_{90} of 1.0 μg/ml, with 84, 97, and 99% of the strains susceptible at breakpoints of 0.5, 1.0, and 2.0 μg/ml, respectively. Two strains (one strain each of *Prevotella bivia* and *Eubacterium lentum*, both with MICs of 4.0 μg/ml) were resistant to CP 99,219 at a preliminary breakpoint of 2.0 μg/ml. By contrast, ciprofloxacin and OPC 17116 were much less active (MIC_{50}, 4.0 μg/ml; MIC_{90}, 32.0 μg/ml and 2.0 and 16.0 μg/ml, respectively). Grepafloxacin yielded MICs that were generally one or two doubling dilutions lower than those obtained with ciprofloxacin. Metronidazole was active against all gram-negative rods (MIC_{90}, 4.0 μg/ml), but 19% of the peptostreptococci, 66% of the gram-positive non-spore-forming rods, and 13% of the clostridia were resistant at >8.0 μg/ml. Ten of the 12 metronidazole-resistant gram-positive cocci were strict anaerobes; the other two were strains of *Streptococcus intermedius*. At the new lower breakpoint of 16.0 μg/ml, cefoxitin was active against 84.0% of all strains, with an overall MIC_{50} of 4.0 μg/ml and a MIC_{90} of 32.0 μg/ml.

Tazobactam enhanced the activity of piperacillin against >95% of β-lactamase-producing gram-negative anaerobic rods, with the MIC_{90} lowered from 256.0 μg/ml to 16.0 μg/ml. All gram-positive strains (β-lactamase negative) were susceptible to piperacillin (MIC_{90}, 4.0 μg/ml).

CP 99,219 is a new trifluoronaphthyridone with antibacterial activity that includes members of the family *Enterobacteriaceae*, *Moraxella catarrhalis*, *Haemophilus influenzae*, gonococci, *Legionella* species, *Pseudomonas aeruginosa*, *Xanthomonas maltophilia*, ciprofloxacin-susceptible and -resistant staphylococci and streptococci, most enterococci, *Leuconostoc* species, and lactobacilli (10, 13). In humans, mean values for the maximum drug concentration in serum were 0.3, 1.5, 4.4, 6.6, and 10.1 μg/ml for single oral doses of 30, 100, 300, 600, and 1,000 mg, respectively (23). CP 99,219 showed activity similar to that of clindamycin and was significantly more potent than ciprofloxacin, cefoxitin, and metronidazole in a mouse model of *B. fragilis* and *Staphylococcus aureus* localized mixed infection (11).

The activity of CP 99,219 against *B. fragilis* in a previous preliminary report parallels the findings in the current study (14). The MIC_{90} of >8.0 μg/ml for CP 99,219 against *B. fragilis* reported in the paper by Gooding and Jones (13) represents an error; the MIC_{90} was, in actuality, 0.5 μg/ml (16), which is similar to values reported in this study.

Of the other agents tested in this study, the following points should be noted. We found slightly improved anti-anaerobic activity of grepafloxacin compared with ciprofloxacin, confirming findings reported by Ueno and colleagues (25). Susceptibility spectra of cefoxitin, piperacillin, and piperacillin-tazobactam parallel previous results (4). Resistance to metronidazole in gram-positive anaerobes other than non-spore-forming rods has also been reported previously (4). This study confirms the excellent anti-anaerobic activity of metronidazole against gram-negative anaerobic rods and of piperacillin-tazobactam against all anaerobe groups (4).

The excellent activity of CP 99,219 against all clinically significant anaerobe groups reported in this study, coupled with promising pharmacokinetic and animal model results, point to clinical trials with an oral and/or parenteral form of CP 99,219 used for treatment of mixed aerobic and anaerobic infections.

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