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Comparative Activity of Ciprofloxacin, Ofloxacin, Sparfloxacin, Temafloxacin, CI-960, CI-990, and WIN 57273 against Anaerobic Bacteria

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The in vitro activities of seven fluoroquinolones against 290 anaerobes were determined by agar dilution. CI-960 and WIN 57273 inhibited >95% of the strains at ≤2 μg/ml. CI-990 required ≤16 μg/ml. Clustering around 2 to 4 μg/ml was noted for *Bacteroides fragilis* group organisms with CI-990, sparfloxacin, and temafloxacin. Temafloxacin and sparfloxacin inhibited most strains at ≤2 μg/ml. *B. fragilis* was more susceptible to all quinolones than were the other *B. fragilis* group strains.

The activity of fluoroquinolones against anaerobic bacteria has been reported to be moderate to poor (2, 3, 5–9, 11, 13, 15, 16, 18, 19). Consequently, industry has attempted to synthesize new compounds with improved antianaerobic activity (5). We evaluated the activities of seven fluoroquinolone compounds against 290 recent clinical anaerobic isolates and three American Type Culture Collection (ATCC) strains.

The anaerobic bacteria studied (Table 1) were 1990 isolates from two primary-care community hospitals and were identified by standard criteria (4, 10, 17). Standard powders were kindly supplied as follows: ciprofloxacin, Miles Laboratories, West Haven, Conn.; ofloxacin, R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.; sparfloxacin (AT-4140, RP 64206, and PD 131501), CI-960 (PD 127391 and AM 1091) [7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid], and CI-990 (PD 131,628) [(*S*)-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid], Parke-Davis Pharmaceutical Research Division of Warner Lambert Co., Ann Arbor, Mich.; temafloxacin, Abbott Laboratories, North Chicago, Ill.; and WIN 57273 [1-cyclopropyl-7-(2,6-dimethyl-4-pyridinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid], Sterling Winthrop Co., Rensselaer, N.Y. Isolate susceptibility was determined by the Wadsworth agar dilution method in accordance with National Committee for Clinical Laboratory Standards guidelines (14, 17). Plates were inoculated with a Steers replicator (Craft Machine Inc., Chester, Pa.) to give a final inoculum of 10^5 CFU per spot. *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, and *Eubaterium lentum* ATCC 43055 were included as controls.

The results are shown in Tables 1 and 2. All *Bacteroides ureolyticus*, *Clostridium perfringens*, *Bilophila wadsworthia* (three strains), *Fusobacterium nucleatum*, *Fusobacterium necrophorum*, *Eubacterium* species (four strains), and *Propionibacterium* species strains were inhibited by ≤2 μg of all of the agents tested per ml. CI-960 and WIN 57273 were active at ≤2 μg/ml against >95% of all of the strains tested. For one strain each of *Bacteroides caccae*, *Clostridium ramosum*, and *Prevotella melaninogenica*, the MIC of CI-960 was >4 μg/ml. One strain each of *Clostridium limosum* and *Fusobacterium gonidiaformans* and two of *P. melaninogenica* were resistant to WIN 57273. Temafloxacin was active against 91% of *B. fragilis* strains, but several strains of *Bacteroides distasonis*, *Bacteroides thetaiotaomicron*, *Bacteroides vulgatus*, and *Bacteroides uniformis* were resistant to >4 μg/ml. For many non-*perfringens Clostridium* species, non-spore-forming gram-positive bacilli, and *Fusobacterium varium*, *Fusobacterium mortiferum*, and *Fusobacterium ulcerans* strains, the temafloxacin MICs were >4 μg/ml. Of the *B. fragilis* species and *B. fragilis* group species, the sparfloxacin MIC for 13 and 16%, respectively, was >4 μg/ml. For only 17% of *Prevotella bivia* strains and 57% of *P. melaninogenica* strains, the sparfloxacin MICs were ≤4 μg/ml. The MICs for all strains of *F. varium* and *F. ulcerans* were >4 μg/ml. While all *C. perfringens* isolates were susceptible to ≤0.5 μg of sparfloxacin per ml, the other clostridia were more resistant, with MICs for 90% of the strains tested (MIC_{90}s) of 8 and 32 μg/ml. Sparfloxacin was less active against *P. bivia*, *F. varium*, *F. ulcerans*, and *P. melaninogenica*, often requiring 8 to 16 μg/ml for inhibition.

CI-990 was active against all peptostreptococci and 87% of *B. fragilis* species at ≤2 μg/ml, but 28% of other *B. fragilis* group species required >4 μg/ml for inhibition. Clustering around a concentration of 2 to 4 μg/ml was found. MICs against *F. varium* and *F. ulcerans* were higher, with clustering around 2 to 4 μg/ml, resulting in 69% resistance. Ninety-two percent of *P. bivia* isolates were resistant (MIC, >4 μg/ml) to CI-990.

B. fragilis species were generally more susceptible to all of the agents tested than were other members of the *B. fragilis* group. *F. varium* was the most resistant of the fusobacteria, *P. bivia* was the most resistant *Prevotella* species, and *Clostridium clostridiiforme* was the most resistant *Clostridium* species tested. Clustering around the proposed breakpoints was noted for the *B. fragilis* group with CI-990, sparfloxacin, and temafloxacin. Lactobacilli and *Veillonella* species (five strains of each) showed various susceptibilities.

In 1988, Phillips and King (16) compared the activities of the 4-quinolones and noted that difloxacin, A-56620, ciprofloxacin, ofloxacin, enoxacin, norfloxacin, pefloxacin, CI-934, and nalidixic acid had modest anaerobic activity. Our study showed that two new quinolones, CI-960 and WIN 57272, were the most active, and almost all of the 290

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TABLE 1. Comparative activities of ciprofloxacin, ofloxacin, sparfloxacin, temafloxacin, CI-960, CI-990, and WIN 57273 against 290 clinical isolates of anaerobic bacteria

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates susceptible at[a]:		
	Range	50%[b]	90%[b]	Concn 1	Concn 2	Concn 3
Actinomyces sp. (5)[c]						
Ciprofloxacin	<0.06–16	8		20	20	40
Ofloxacin	0.125–8	8		20	40	80
Sparfloxacin	<0.03–4	4		20	20	100
Temafloxacin	<0.03–8	4		20	80	100
CI-960	<0.015–1	0.5		100	100	100
CI-990	<0.03–4	4		20	20	100
WIN 57273	<0.015–0.5	0.25		100	100	100
Bacteroides caccae (10)						
Ciprofloxacin	8–>128	16	32	0	0	0
Ofloxacin	1–>128	8	8	10	40	90
Sparfloxacin	0.125–32	2	4	30	80	90
Temafloxacin	0.25–64	2	4	80	90	90
CI-960	0.03–8	0.125	0.25	90	90	90
CI-990	1–32	2	4	10	50	90
WIN 57273	0.06–4	0.25	0.5	100	100	100
Bacteroides distasonis (12)						
Ciprofloxacin	2–64	4	32	0	8	58
Ofloxacin	2–64	2	16	58	83	83
Sparfloxacin	1–16	2	4	33	75	92
Temafloxacin	2–32	2	16	50	75	92
CI-960	0.06–2	0.125	1	92	100	100
CI-990	2–32	2	16	0	50	83
WIN 57273	0.25–1	0.5	0.5	100	100	100
Bacteroides fragilis (23)						
Ciprofloxacin	2–>128	4	8	0	9	67
Ofloxacin	2–64	2	8	78	87	91
Sparfloxacin	0.5–16	1	4	61	87	91
Temafloxacin	1–32	1	4	87	91	91
CI-960	0.06–2	0.125	0.5	96	100	100
CI-990	1–16	2	4	43	87	91
WIN 57273	0.125–2	0.25	0.5	100	100	100
Bacteroides ovatus (10)						
Ciprofloxacin	8–64	16	16	0	0	0
Ofloxacin	8–16	16	16	0	0	40
Sparfloxacin	1–4	2	4	20	80	100
Temafloxacin	2–4	4	4	40	100	100
CI-960	0.125–0.5	0.125	0.25	100	100	100
CI-990	2–8	4	4	0	40	90
WIN 57273	0.25–1	0.5	1	100	100	100
Bacteroides thetaiotaomicron (17)						
Ciprofloxacin	8–128	16	64	0	0	0
Ofloxacin	4–128	8	128	0	12	82
Sparfloxacin	0.5–16	2	8	12	82	82
Temafloxacin	2–32	2	32	59	82	82
CI-960	0.125–2	0.25	2	82	100	100
CI-990	1–16	2	16	6	76	82
WIN 57273	0.25–2	0.5	2	100	100	100
Bacteroides uniformis (12)						
Ciprofloxacin	2–64	8	16	0	8	25
Ofloxacin	2–8	4	8	33	67	100
Sparfloxacin	0.5–8	2	4	33	67	92
Temafloxacin	0.5–16	2	8	58	83	92
CI-960	0.06–2	0.25	0.5	92	100	100
CI-990	1–8	4	8	17	33	83
WIN 57273	0.06–0.5	0.25	0.5	100	100	100

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TABLE 1—*Continued*

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates susceptible at[a]:		
	Range	50%[b]	90%[b]	Concn 1	Concn 2	Concn 3
Bacteroides vulgatus (12)						
Ciprofloxacin	4–128	16	64	0	0	8
Ofloxacin	1–16	2	16	67	75	92
Sparfloxacin	0.5–2	1	2	75	100	100
Temafloxacin	0.5–8	0.5	2	92	92	100
CI-960	0.06–1	0.06	0.5	100	100	100
CI-990	2–16	2	16	0	50	75
WIN 57273	0.03–0.5	0.06	0.125	100	100	100
Bacteroides ureolyticus group (11)[d]						
Ciprofloxacin	<0.06–0.25	<0.06	0.25	100	100	100
Ofloxacin	<0.06–1	0.125	0.5	100	100	100
Sparfloxacin	<0.015–1	0.06	0.5	100	100	100
Temafloxacin	<0.015–2	0.125	1	100	100	100
CI-960	<0.015–0.5	<0.015	0.06	100	100	100
CI-990	<0.015–0.125	0.03	0.125	100	100	100
WIN 57273	<0.015–0.5	0.5	0.5	100	100	100
Other *Clostridium* spp. (23)[e]						
Ciprofloxacin	0.5–32	2	16	22	52	70
Ofloxacin	0.5–32	4	16	48	61	83
Sparfloxacin	0.25–16	2	8	30	70	83
Temafloxacin	0.25–16	2	16	74	83	87
CI-960	0.03–1	0.25	0.5	100	100	100
CI-990	0.25–16	1	4	61	74	95
WIN 57273	≤0.015–8	0.125	0.5	96	96	100
Clostridium perfringens (12)						
Ciprofloxacin	0.25–0.5	0.5	0.5	100	100	100
Ofloxacin	0.5–1	0.5	0.5	100	100	100
Sparfloxacin	0.125–0.5	0.25	0.5	100	100	100
Temafloxacin	0.125–0.5	0.25	0.5	100	100	100
CI-960	0.06–0.125	0.06	0.125	100	100	100
CI-990	0.125–0.25	0.125	0.25	100	100	100
WIN 57273	≤0.015–0.06	≤0.015	0.03	100	100	100
Clostridium ramosum-C. innocuum-C. clostridiiforme group (15)						
Ciprofloxacin	1–>128	8	64	7	7	20
Ofloxacin	1–>128	16	128	7	7	47
Sparfloxacin	0.25–32	4	32	20	33	53
Temafloxacin	0.5–64	4	32	40	53	60
CI-960	0.125–8	0.5	2	87	93	93
CI-990	<0.06–64	2	32	27	60	67
WIN 57273	0.06–2	0.25	2	100	100	100
Other *Fusobacterium* spp. (20)[f]						
Ciprofloxacin	0.5–16	2	8	35	90	90
Ofloxacin	0.5–64	2	16	85	90	90
Sparfloxacin	0.5–8	2	8	35	85	90
Temafloxacin	0.125–8	0.5	8	75	90	100
CI-960	0.03–0.5	0.06	0.5	100	100	100
CI-990	0.25–8	1	4	85	90	95
WIN 57273	0.03–1	0.06	1	100	100	100
Fusobacterium varium-F. ulcerans-F. gonidiaformans group (14)						
Ciprofloxacin	2–32	8	16	0	7	7
Ofloxacin	2–128	8	16	7	7	50
Sparfloxacin	4–32	16	16	0	0	7
Temafloxacin	2–32	8	16	7	7	64
CI-960	0.125–2	0.5	1	93	100	100
CI-990	2–8	4	4	7	29	93
WIN 57273	0.125–32	2	2	93	93	93

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TABLE 1—*Continued*

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% of isolates susceptible at[a]:		
	Range	50%[b]	90%[b]	Concn 1	Concn 2	Concn 3
Peptostreptococcus sp. (22)[g]						
Ciprofloxacin	0.125–8	1	4	59	86	91
Ofloxacin	0.125–16	0.5	8	59	86	91
Sparfloxacin	0.06–4	0.25	1	91	91	100
Temafloxacin	0.06–2	0.25	2	100	100	100
CI-960	≤0.015–0.5	0.03	0.5	100	100	100
CI-990	0.03–2	0.25	2	86	100	100
WIN 57273	≤0.015–0.25	0.03	0.125	100	100	100
Prevotella bivia (12)						
Ciprofloxacin	4–16	16	16	0	0	8
Ofloxacin	2–8	8	8	17	25	100
Sparfloxacin	2–16	4	16	0	17	58
Temafloxacin	2–8	4	4	25	92	100
CI-960	0.25–0.5	0.25	0.5	100	100	100
CI-990	2–8	8	8	0	8	8
WIN 57273	0.25–0.5	0.5	0.5	100	100	100
Pigmented *Porphyromonas-Prevotella* spp. (17)[h]						
Ciprofloxacin	<0.06–64	1	16	62	81	86
Ofloxacin	0.25–64	1	16	76	86	90
Sparfloxacin	<0.03–32	2	16	33	86	90
Temafloxacin	<0.03–64	1	16	86	90	90
CI-960	0.03–4	0.06	0.25	95	95	100
CI-990	<0.03–8	1	2	67	95	95
WIN 57273	0.06–16	0.25	0.5	90	90	95
Other, nonpigmented *Prevotella* spp. (14)[i]						
Ciprofloxacin	1–4	2	2	21	93	100
Ofloxacin	1–2	2	2	100	100	100
Sparfloxacin	1–2	2	2	29	100	100
Temafloxacin	1–2	1	2	100	100	100
CI-960	0.03–0.125	0.03	0.06	100	100	100
CI-990	0.25–2	1	1	93	100	100
WIN 57273	0.125–0.5	0.25	0.5	100	100	100
Propionibacterium sp. (11)[j]						
Ciprofloxacin	0.25–1	0.25	0.5	100	100	100
Ofloxacin	0.25–0.5	0.5	0.5	100	100	100
Sparfloxacin	0.06–0.25	0.25	0.25	100	100	100
Temafloxacin	0.125–0.25	0.25	0.25	100	100	100
CI-960	0.03–0.06	0.03	0.06	100	100	100
CI-990	0.125–0.5	0.5	0.5	100	100	100
WIN 57273	<0.015–0.03	0.03	0.03	100	100	100

[a] Concentrations 1, 2, and 3, respectively, were 1, 2, and 4 μg/ml for ciprofloxacin, sparfloxacin, CI-960, and CI-990 and 2, 4, and 8 μg/ml for ofloxacin, temafloxacin, and WIN 57273.
[b] 50% and 90%, concentrations of antimicrobial agents required to inhibit 50 and 90% of the strains, respectively.
[c] One *A. israelii*, one *Actinomyces* VPI group 1, two *A. meyerii* and one *A. odontolyticus* isolate.
[d] Three *B. gracilis*, six *B. ureolyticus*, and two *Wolinella recta* isolates.
[e] Four *C. bifermentans*, three *C. butyricum*, one *C. cadaveris*, three *C. difficile*, one *C. limosum*, three *C. paraputrificum*, two *C. sordelii*, three *C. subterminale*, one *C. symbiosum*, and two *C. tertium* isolates.
[f] Six *F. mortiferum*, ten *F. necrophorum*, four *F. nucleatum* isolates.
[g] Four *P. anaerobius*, five *P. asaccharolyticus*, four *P. micros*, four *P. magnus*, and five *P. prevotii* isolates.
[h] Two *P. asaccharolytica*, two *P. gingivalis*, six *P. intermedia*, and seven *P. melaninogenica* isolates.
[i] Seven *P. buccae* and seven *P. oralis* isolates.
[j] Five *P. acnes*, three *P. avidum*, and three *P. granulosum* isolates.

isolates from the 12 genera and 52 species tested were susceptible to ≤2 μg/ml. As reported previously (8, 16, 19), ciprofloxacin had relatively poor activity.

King et al. (12) tested CI-960 (PD 127391) and found that "differences in susceptibility between the *Bact. fragilis* group were minimal but *Bact. ovatus* and *Bact. uniformis* were the least sensitive." We noted that all of the *B. fragilis* group species were very susceptible to CI-960 but *B. thetaiotaomicron*, for which the MIC_{90} was 2 μg/ml, was the least susceptible. In accord with others studies (6, 11), most of our isolates were also very susceptible to WIN 57273, but we encountered resistance in four strains (*P. melaninogenica*,

TABLE 2. MICs obtained for ATCC control strains on supplemented brucella agar

Drug	MIC range (mode; μg/ml)		
	B. fragilis ATCC 25285	*B. thetaiotaomicron* ATCC 29741	*E. lentum* ATCC 43055
Ciprofloxacin	2–2 (2)	16–16	0.5–2 (1)
Ofloxacin	1–2 (2)	8–8	1–1 (1)
CI-960	0.06–0.06 (0.06)	0.25–0.25	0.03–0.06 (0.06)
CI-990	1–1 (1)	2–2	0.5–0.5 (0.5)
Sparfloxacin	1–2 (1)	2–2	1–1 (1)
Temafloxacin	0.5–1 (0.5)	2–4	0.5–1 (0.5)
WIN 57273	0.25–0.25 (0.25)	0.25–0.25	0.06–0.25 (0.125)

C. limosum, and *F. gonidiaformans*), and several other strains, including isolates of *B. caccae*, *B. distasonis*, *B. fragilis*, *B. thetaiotaomicron*, *F. varium*, *F. ulcerans*, and *Veillonella* species, required up to 2 μg/ml for inhibition.

Studies of the efficacy of sparfloxacin against anaerobes have used diverse methods and inocula (1, 3, 13, 18). By using an agar dilution method, brucella blood agar, and a 10^5 CFU inoculum, we showed slightly different results with species variation among *B. fragilis* group isolates. We also noted clustering at concentrations of 2 to 4 μg/ml for *B. fragilis* but not the other *B. fragilis* group species. Sparfloxacin had MIC_{90}s of 4 μg/ml for *B. fragilis*, *B. caccae*, *B. distasonis*, and *B. ovatus* but 2 μg/ml for *B. vulgatus* and 8 μg/ml for *B. thetaiotaomicron*. Temafloxacin and CI-990 were similar in their spectra of activity against anaerobic bacteria. CI-990 was more active than temafloxacin against the *B. ureolyticus* group, some clostridia, some fusobacteria, lactobacilli, and pigmented *Prevotella-Porphyromonas* species, while temafloxacin was more active against *B. vulgatus* and *P. bivia*. Our temafloxacin data for *B. fragilis* (MIC_{90}, 4 μg/ml) and *C. perfringens* (MIC_{90}, 0.5 μg/ml) were the same as those of Hardy et al. (9), who used Wilkins-Chalgren agar. Comparatively, our strains of peptostreptococci were more susceptible (MIC_{90}, 0.25 versus 2 μg/ml) but we could not compare their "other *Bacteroides* species" group owing to lack of species identification data. Cohen et al. (5) recently tested PD 131628, the active metabolite of the prodrug L-ananyl aminde, PD 131112 (CI-990), against 41 anaerobic bacteria by using a broth microdilution method and showed it to be active at ≤4 μg/ml against *B. fragilis* group species. Our data showed that the CI-990 MIC_{90} was 4 μg/ml for *B. fragilis*, *B. caccae*, and *B. ovatus* strains but *B. distasonis*, *B. thetaiotaomicron*, and *B. vulgatus* strains were more resistant (MIC_{90}, 16 μg/ml).

Isolates included strains variously susceptible to clindamycin, cefoxitin, and piperacillin. No relationship between resistance to those agents and resistance to the fluoroquinolones was noted. One *B. fragilis* strain resistant to imipenem (MIC, >128 μg/ml) and all beta-lactams was susceptible to all quinolones except ciprofloxacin. For strains for which the MIC of any fluoroquinolone was increased, the MICs of the others were quantitatively similarly increased.

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