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Comparative In Vitro Activities of Trovafloxacin (CP 99,219) and Other Antimicrobials against Clinically Significant Anaerobes

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A total of 590 strains of clinically important anaerobes were tested to determine their susceptibility to trovafloxacin. Overall, trovafloxacin had a mode MIC of 0.25 μg/ml and a MIC at which 90% of the isolates were inhibited of 1 μg/ml and had activity comparable to that of metronidazole. Trovafloxacin was 8-, 8-, 16-, 32-, and 64-fold more active than ampicillin-sulbactam, clindamycin, ciprofloxacin, cefoxitin, and cefotetan, respectively. Of the *Bacteroides fragilis* group, 97% of the isolates were inhibited by trovafloxacin at 2 μg/ml, and trovafloxacin was more active than ciprofloxacin, cefoxitin, cefotetan, ampicillin-sulbactam, and clindamycin against *Clostridium*, *Fusobacterium*, *Porphyromonas*, and *Prevotella* strains.

The development of fluoroquinolone antimicrobials heralded a new group of antimicrobial agents against which there were only very low rates of resistance among many clinically important strains of bacteria. These potent agents were highly active against most members of the family *Enterobacteriaceae*, including strains resistant to multiple antimicrobial agents. Fluoroquinolones have not been recommended for therapy of mixed aerobic-anaerobic infections because of the relatively poor activity of these agents against anaerobes. Newer fluoroquinolones, such as Bay Y3118 and WIN 57273, have increased antianaerobic activity but have not been developed due to toxicity (1, 6). The present report details the in vitro activity of trovafloxacin, a new trifluoronaphthyridone agent, against clinical isolates of the *Bacteroides fragilis* group and other anaerobes compared to those of ciprofloxacin and other antimicrobial agents.

A total of 590 clinical strains of anaerobes were tested and consisted of *B. fragilis* (229 strains), *Bacteroides distasonis* (46 strains), *Bacteroides ovatus* (41 strains), *Bacteroides thetaiotaomicron* (68 strains), *Bacteroides uniformis* (17 strains), *Bacteroides vulgatus* (35 strains), *Bacteroides capillosus* (14 strains), *Prevotella bivia* (20 strains), *Prevotella disiens* (14 strains), *Porphyromonas asaccharolytica* (11 strains), *Prevotella melaninogenica* (10 strains), *Fusobacterium* spp. (14 strains), *Clostridium perfringens* (10 strains), *Clostridium* spp. (14 strains), *Eubacterium lentum* (10 strains), *Peptostreptococcus* spp. (14 strains), and *Veillonella parvula* (10 strains). A group of 13 *B. fragilis* group strains previously shown to be resistant to imipenem (MICs, 16 to ≥32 μg/ml) were also tested. All isolates were identified by using selective media, biochemical profiles, and gas-liquid chromatography (8, 11).

Laboratory standard powders were provided by the following manufacturers: trovafloxacin, ampicillin, doxycycline, and sulbactam, Pfizer Inc., New York, N.Y.; ciprofloxacin, Miles Pharmaceuticals, West Haven, Conn.; cefoxitin, Merck Sharp & Dohme, Rahway, N.J.; cefotetan, Zeneca, Wilmington, Del.; clindamycin, Upjohn, Kalamazoo, Mich.; and metronidazole, G.D. Searle, Skokie, Ill. All powders were stored desiccated at −20°C until use.

Each strain was tested by the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (9). Serial twofold dilutions of each antimicrobial agent (or combination) were prepared in anaerobe broth MIC (Difco) within a dilution scheme of 0.015 to 256 μg/ml. For fastidious isolates, which included isolates of *Fusobacterium*, *Porphyromonas*, and *Peptostreptococcus*, the test medium was supplemented with 5% laked horse blood. When ampicillin was combined with sulbactam, a 2:1 ratio was used. The inoculum was prepared by suspending colonies from an overnight blood agar plate in 5 ml of prereduced anaerobe broth MIC equivalent to a no. 1 McFarland standard and was further diluted to give a final inoculum size of 10^5 CFU per well (10^6 CFU/ml). All plates were incubated for 48 h at 35°C anaerobically and then read. The MIC was defined as the lowest concentration of each antimicrobial agent which inhibited visible growth of the test isolate. With each susceptibility run, quality control was performed with *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *E. lentum* ATCC 43055.

Twenty-three strains of the *B. fragilis* group were tested at three different inoculum sizes against trovafloxacin and ciprofloxacin. The inoculum was prepared by diluting each organism suspension to give final inoculum sizes of 10^3, 10^5, and 10^7 CFU per well. With each test run, colony counts on a single strain were performed to verify the inoculum sizes. Fifty isolates of the *B. fragilis* group were tested at three different pHs to determine differences in the activities of trovafloxacin and ciprofloxacin. The pH adjustments were made when the test plates were prepared, and the inoculum size was 10^5 CFU per well. Ten isolates of the *B. fragilis* group were tested to determine the effects of various protein concentrations on the activities of trovafloxacin and ciprofloxacin. Susceptibility trays containing 0, 5, 10, 20, and 40 mg% of human serum albumin were prepared in duplicate, and were inoculated with 10^5 CFU per well. The inoculated plates for all of the test conditions described above were incubated anaerobically at 35°C for 48 h, and the MICs were determined as previously described.

Table 1 compares the in vitro activities of the various antimicrobial agents against the test isolates. Overall, trovafloxacin was the most active agent, inhibiting 91, 97, and 99.5% of the strains at 1, 2, and 4 μg/ml. Ciprofloxacin was 16-fold (MIC at which 90% of the isolates were inhibited [MIC_{90}], 1 versus 16 μg/ml) less active and inhibited 4, 23, and 54% of the isolates

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TABLE 1. Comparison of the in vitro activities of trovafloxacin and other antimicrobials against the *B. fragilis* group and other anaerobes[a]

Strain and antimicrobial[b]	Range	Mode MIC	MIC_{50}	MIC_{90}
B. fragilis (229)				
Trovafloxacin	0.03–2[b]	0.25	0.25	0.5
Ciprofloxacin	0.25–≥16	4	4	16
Cefoxitin	0.12–≥128	8	8	16
Cefotetan	0.12–≥128	8	8	16
Doxycycline	0.03–16	2	2	4
Ampicillin-sulbactam	0.03–≥64	1	2	8
Clindamycin	0.03–≥16	0.5	0.5	2
Metronidazole	≤0.12–8	1	1	2
B. thetaiotaomicron (68)				
Trovafloxacin	0.06–4	0.5	0.5	1
Ciprofloxacin	1–16	16	16	16
Cefoxitin	1–64	16	16	32
Cefotetan	0.5–128	32	32	64
Doxycycline	0.03–8	2	2	4
Ampicillin-sulbactam	1–32	2	2	8
Clindamycin	0.06–16	1	2	16
Metronidazole	0.12–4	1	1	2
B. distasonis (46)				
Trovafloxacin	0.12–2	0.5	0.5	0.5
Ciprofloxacin	1–16	4	4	8
Cefoxitin	4–64	8	16	32
Cefotetan	1–128	128	32	128
Doxycycline	0.03–8	2	2	4
Ampicillin-sulbactam	1–64	4	4	16
Clindamycin	0.03–16	2	2	8
Metronidazole	0.12–4	1	1	2
B. ovatus (41)				
Trovafloxacin	0.12–4	0.5	0.5	1
Ciprofloxacin	1–16	8	8	16
Cefoxitin	2–128	16	16	32
Cefotetan	1–128	32	32	128
Doxycycline	0.03–8	2	2	4
Ampicillin-sulbactam	0.5–64	2	2	16
Clindamycin	0.25–16	2	2	16
Metronidazole	0.25–4	1	1	2
B. vulgatus (35)				
Trovafloxacin	0.12–8	0.12	0.12	4
Ciprofloxacin	0.25–16	16	16	16
Cefoxitin	0.25–64	2	2	64
Cefotetan	0.25–128	2	4	128
Doxycycline	0.03–8	4	4	4
Ampicillin-sulbactam	0.5–16	1	2	16
Clindamycin	0.03–16	0.5	0.5	16
Metronidazole	0.12–1	0.5	0.5	1
B. uniformis (17)				
Trovafloxacin	0.25–4	0.5	0.5	4
Ciprofloxacin	0.25–16	16	16	16
Cefoxitin	0.5–64	1	2	64
Cefotetan	0.5–128	8	8	128
Doxycycline	0.06–4	4	4	4
Ampicillin-sulbactam	0.25–8	2	2	8
Clindamycin	0.015–16	1	1	4
Metronidazole	0.12–1	0.5	0.5	1
B. fragilis group (cefoxitin susceptible) (409)				
Trovafloxacin	0.03–8	0.25	0.25	1
Ciprofloxacin	0.25–16	4	4	16
Cefoxitin	0.12–32	8	8	16
Cefotetan	0.12–128	8	8	64
Doxycycline	0.03–16	2	2	4
Ampicillin-sulbactam	0.03–64	1	2	8
Clindamycin	0.015–16	0.5	1	8
Metronidazole	0.12–16	1	1	2
B. fragilis group (cefoxitin resistant) (26)				
Trovafloxacin	0.12–4	0.25	0.25	2
Ciprofloxacin	1–16	16	8	16
Cefoxitin	64–128	64	64	128
Cefotetan	1–128	128	128	128
Doxycycline	0.06–8	2	2	8
Ampicillin-sulbactam	4–64	8	16	32
Clindamycin	0.015–16	1	1	16
Metronidazole	0.25–2	0.5	0.5	2
B. fragilis group (imipenem resistant) (13)				
Trovafloxacin	0.015–2	0.015	0.06	1
Ciprofloxacin	2–16	16	4	16
Cefoxitin	32–128	64	64	64
Cefotetan	32–128	128	128	128
Doxycycline	2–4	2	2	4
Ampicillin-sulbactam	32–64	32	64	64
Clindamycin	0.5–16	2	2	16
Metronidazole	0.12–2	2	2	2
B. capillosus (14)				
Trovafloxacin	0.12–2	0.5	0.5	1
Ciprofloxacin	0.5–16	2	2	2
Cefoxitin	1–16	8	4	8
Cefotetan	4–32	8	8	32
Doxycycline	0.03–4	4	4	4
Ampicillin-sulbactam	0.12–4	1	1	2
Clindamycin	0.015–4	0.015	0.015	0.12
Metronidazole	0.5–2	1	1	2
P. bivia (20)				
Trovafloxacin	0.015–1	0.5	0.5	1
Ciprofloxacin	0.12–16	8	4	8
Cefoxitin	0.06–4	0.25	0.5	2
Cefotetan	0.12–16	2	2	4
Doxycycline	0.03–8	4	4	4
Ampicillin-sulbactam	0.03–8	4	1	4
Clindamycin	0.015–0.03	0.015	0.015	0.03
Metronidazole	0.12–2	1	1	2
P. disiens (14)				
Trovafloxacin	0.5–1	0.5	0.5	1
Ciprofloxacin	0.5–2	1	1	2
Cefoxitin	0.12–2	0.5	0.5	2
Cefotetan	0.12–8	2	2	4
Doxycycline	0.03–8	2	2	4
Ampicillin-sulbactam	0.06–4	0.25	0.25	2
Clindamycin	0.015–4	0.015	0.015	0.015
Metronidazole	0.5–2	2	2	2
P. asaccharolytica (11)				
Trovafloxacin	0.015–0.5	0.25	0.5	0.5
Ciprofloxacin	0.03–1	0.5	1	1
Cefoxitin	0.06–8	0.25	1	4
Cefotetan	0.12–16	8	2	8
Doxycycline	0.03–4	2	2	2
Ampicillin-sulbactam	0.03–4	1	0.5	1
Clindamycin	0.015–0.12	0.015	0.015	0.03
Metronidazole	0.25–2	0.5	0.5	2
P. melaninogenica (10)				
Trovafloxacin	0.12–0.5	0.5	0.5	0.5
Ciprofloxacin	0.5–1	1	1	1
Cefoxitin	0.12–2	0.5	0.5	2
Cefotetan	0.12–4	1	1	4
Doxycycline	0.03–4	0.03	0.5	4
Ampicillin-sulbactam	0.06–0.5	0.5	0.25	0.5
Clindamycin	0.06–0.12	0.06	0.06	0.12
Metronidazole	0.12–2	0.5	0.5	2
Fusobacterium spp. (14)[c]				
Trovafloxacin	0.015–2	0.25	0.25	0.5
Ciprofloxacin	0.015–8	1	1	4
Cefoxitin	0.06–2	0.06	0.25	2
Cefotetan	0.06–8	0.06	0.06	2
Doxycycline	0.015–2	0.015	0.03	2

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TABLE 1—*Continued*

Strain and antimicrobial[b]	Range	Mode MIC	MIC_{50}	MIC_{90}
Ampicillin-sulbactam	0.03–2	0.03	0.06	1
Clindamycin	0.015–1	0.015	0.015	0.25
Metronidazole	0.12–2	0.12	0.25	2
Clostridium perfringens (10)				
Trovafloxacin	0.06–0.5	0.12	0.12	0.5
Ciprofloxacin	0.25–4	0.5	0.5	4
Cefoxitin	0.06–1	0.5	0.5	1
Cefotetan	0.06–1	0.06	0.06	1
Doxycycline	0.03–4	0.03	1	4
Ampicillin-sulbactam	0.03–0.25	0.03	0.06	0.25
Clindamycin	0.03–2	0.06	0.06	2
Metronidazole	0.25–4	0.5	1	4
Clostridium spp. (14)[d]				
Trovafloxacin	0.03–2	0.12	0.12	0.5
Ciprofloxacin	0.06–4	0.25	0.5	4
Cefoxitin	0.06–64	2	2	64
Cefotetan	0.06–128	8	1	32
Doxycycline	0.03–0.5	0.03	0.03	0.5
Ampicillin-sulbactam	0.03–4	0.25	0.25	2
Clindamycin	0.03–16	0.03	0.25	8
Metronidazole	0.12–2	0.25	0.25	2
E. lentum (10)				
Trovafloxacin	0.015–0.5	0.12	0.12	0.25
Ciprofloxacin	0.06–2	0.5	0.5	1
Cefoxitin	2–16	8	8	16
Cefotetan	4–64	64	32	64
Doxycycline	0.06–8	0.03	0.03	8
Ampicillin-sulbactam	0.06–4	1	1	4
Clindamycin	0.015–1	0.015	0.25	1
Metronidazole	0.06–0.5	0.06	0.06	0.25
Peptostreptococcus spp. (14)				
Trovafloxacin	0.015–0.5	0.015	0.06	0.5
Ciprofloxacin	0.015–2	2	0.25	2
Cefoxitin	0.06–0.5	0.06	0.06	0.5
Cefotetan	0.06–1	0.06	0.12	1
Doxycycline	0.03–2	2	1	2
Ampicillin-sulbactam	0.03–0.25	0.03	0.12	0.25
Clindamycin	0.015–4	0.015	0.03	0.25
Metronidazole	0.12–1	0.25	0.25	1
V. parvula (10)				
Trovafloxacin	0.015–2	0.06	0.06	0.25
Ciprofloxacin	0.015–2	0.03	0.06	0.25
Cefoxitin	0.06–0.5	0.06	0.12	0.5
Cefotetan	0.06–0.5	0.06	0.06	0.5
Doxycycline	0.03–4	0.03	0.12	4
Ampicillin-sulbactam	0.03–0.25	0.03	0.06	0.12
Clindamycin	0.015–0.06	0.015	0.015	0.03
Metronidazole	0.25–1	0.25	0.5	1

[a] Results are in micrograms per milliliter.
[b] Numbers in parentheses are numbers of strains tested.
[c] Strains tested (numbers of strains in parentheses) were *F. necrophorum* (1), *F. nucleatum* (7), *F. varium* (1), and *Fusobacterium* spp. (5).
[d] Strains tested (numbers of strains in parentheses) were *C. bifermentans* (1), *C. butyricum* (2), *C. cadaveris* (2), *C. clostridioforme* (1), *C. difficile* (1), *C. innocuum* (2), *C. ramosum* (1), *C. septicum* (1), *C. sphenoides* (1), and *C. sporogenes* (2).

at 1, 2, and 4 μg/ml, respectively. Although overall resistance rates for doxycycline, ampicillin-sulbactam, and cefoxitin were low (0.2, 2.8, and 6%, respectively), trovafloxacin was 4-, 8-, and 64-fold more active than these agents, respectively. Trovafloxacin was 64- and 8-fold more active than cefotetan and clindamycin, respectively. No strains were resistant to metronidazole; however, the trovafloxacin mode MIC was 4-fold less than that of metronidazole (mode MIC, 0.25 versus 1 μg/ml).

Among the various species of the *B. fragilis* group, trovafloxacin was most active against strains of *B. fragilis*, *B. thetaiotaomicron*, *B. distasonis*, and *B. ovatus* (MIC_{90}s, 0.5 to 1 μg/ml), while MICs among strains of *B. uniformis* and *B. vulgatus* were higher (MIC_{90}s, 4 μg/ml). In comparisons of MIC_{90}s among the various species, trovafloxacin was 4- to 32-fold more active than ciprofloxacin, 16- to 64-fold more active than cefoxitin, 32- to 256-fold more active than cefotetan, 2- to 32-fold more active than ampicillin-sulbactam, and 4- to 16-fold more active than clindamycin (with the exception of *B. uniformis* strains). Trovafloxacin was more active than metronidazole against strains of *B. fragilis*, *B. thetaiotaomicron*, *B. distasonis*, and *B. ovatus* but was less active against *B. uniformis* and *B. vulgatus.*

The activities of trovafloxacin against cefoxitin-resistant versus cefoxitin-susceptible *B. fragilis* group strains were virtually the same, inhibiting 92 versus 97% at 2 μg/ml and 100 versus 99.5% at 4 μg/ml, respectively. By comparison, the activities of cefotetan and ampicillin-sulbactam against cefoxitin-resistant strains were reduced. Interestingly, doxycycline was less active against cefoxitin-resistant strains. Additionally, the range of MICs for trovafloxacin among a group of *B. fragilis* group isolates with resistance to imipenem for which the MICs were 16 to ≥32 μg/ml was similar to those of imipenem-susceptible strains.

Trovafloxacin inhibited all strains of *B. capillosus* at 2 μg/ml, while all strains of *P. bivia* and *P. disiens* were inhibited at 1 μg/ml. For nonquinolone agents, only resistance to doxycycline among these three groups of pathogens was detected. Against fastidious strains of *P. asaccharolytica* and *Fusobacterium* spp., trovafloxacin was two- to eightfold more active than ciprofloxacin. No resistance to the other comparative agents was detected.

Trovafloxacin inhibited all strains of *C. perfringens* at a concentration of 0.5 μg/ml, while 2 μg of trovafloxacin per ml was needed to inhibit all other *Clostridium* strains. With the exception of cefotetan, all agents showed good activity against strains of *E. lentum*; all strains were inhibited by trovafloxacin at ≤1 μg/ml. All strains of *Peptostreptococcus* spp. and *V. parvula* were inhibited at 1 and 2 μg/ml of trovafloxacin, respectively; no resistance was detected to any of the nonquinolone antimicrobials.

Table 2 compares the MIC results for trovafloxacin and ciprofloxacin at the various test conditions. For trovafloxacin, inoculum sizes of 10^3 and 10^5 CFU per well showed identical MIC results; however, a fourfold increase in the MIC between an inoculum size of 10^5 and 10^7 CFU per well was noted. In contrast, ciprofloxacin showed poor activity at all inoculum sizes. Trovafloxacin remained very active at all pH values compared to the poor activity of ciprofloxacin at each pH. Increasing amounts of human serum albumin had little effect on the activity of either trovafloxacin or ciprofloxacin, although for trovafloxacin, a fourfold increase in MIC_{50}s and MIC_{90}s between 0 and 40 mg% was noted.

The new trifluoronaphthyridone trovafloxacin has been shown by investigators to be active against a variety of organisms, including *Enterobacteriaceae*, *Haemophilus influenzae*, *Legionella* spp., *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, staphylococci, streptococci, *Stenotrophomonas maltophilia*, and *Chlamydia* strains (4, 7). Overall, these studies have reported that trovafloxacin is more active than ciprofloxacin.

TABLE 2. Comparison of the effects of inoculum size, pH, and protein concentrations on the activities of trovafloxacin and ciprofloxacin against strains of the *B. fragilis* group[a]

Factor	Trovafloxacin		Ciprofloxacin	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Inoculum size[b]				
10^3	0.25[b]	0.5	8	>16
10^5	0.5	0.5	16	>16
10^7	2	4	>16	>16
pH				
6	1	2	16	>16
7	0.5	0.5	16	>16
8	0.25	0.5	8	>16
Albumin concn[c]				
0	0.5	1	16	64
5	1	2	16	64
10	1	2	16	64
20	1	2	16	64
40	2	4	16	64

[a] All results are in micrograms per milliliter.
[b] Inoculum sizes are given as CFUs per microdilution well.
[c] Albumin concentrations are in milligrams percent.

The present report has compared the in vitro antianaerobic activities of trovafloxacin with those of other agents. Overall, trovafloxacin was active against all of the groups of anaerobes tested; MICs of ≥4 μg/ml against only a few *B. fragilis* group strains were seen. By comparison, trovafloxacin was 2- to 16-fold more active than ciprofloxacin and 2-fold more active than metronidazole overall. Against the *B. fragilis* group, trovafloxacin was 8-, 64-, and 64-fold more active than ampicillin-sulbactam, cefoxitin, and cefotetan, respectively. Using agar dilution methodology, Spangler et al. (10) reported on the activity of trovafloxacin against various groups of anaerobes. For comparable test isolates, our results agree with theirs, with the exception that our strains of *B. vulgatus* were more resistant to trovafloxacin. Child et al. (3) also reported results similar to ours when strains of *B. fragilis* were tested by the agar dilution method. Trovafloxacin also exhibited good activity against other groups of anaerobic bacilli and cocci. Similarly to other fluoroquinolones, trovafloxacin was shown to have a moderate increase in MIC with high inoculum size and to have better activity at a neutral or basic pH (2, 13). Trovafloxacin has a level of serum protein binding higher than those of other fluoroquinolones (70 versus <50%), which probably accounts for the gradual increase in MICs at higher serum albumin levels (12). However, even at the 70% binding level, this probably has little or no effect on in vivo efficacy, since trovafloxacin has been shown to be effective in a mouse model of *B. fragilis* infections (5). This new quinolone agent may be useful in mixed aerobic-anaerobic infections; however, additional in vitro, pharmacodynamic, and animal model studies need to be performed.

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