

Activities of Gatifloxacin Compared to Those of Seven Other Agents against Anaerobic Organisms

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The agar dilution MIC was used to compare activities of gatifloxacin with those of ciprofloxacin, sparfloxacina, trovafloxacin, ampicillin, ampicillin-sulbactam, clindamycin, and metronidazole against 351 anaerobes. Overall MICs at which 50% of the isolates are inhibited and MICs at which 90% of the isolates are inhibited (in micrograms per milliliter) were as follows: gatifloxacin, 0.5 and 4; ciprofloxacin, 2 and 32; sparfloxacina, 2 and 8; trovafloxacin, 1 and 4; ampicillin, 1 and 64; ampicillin-sulbactam, 0.5 and 4; clindamycin, 0.125 and 8; and metronidazole, 1 and >16, respectively. Gatifloxacin MICs were similar to those of trovafloxacin in all organism groups.

Anaerobes are becoming increasingly resistant to β -lactams due to β -lactamase production and other mechanisms. Although β -lactamase production, as well as concomitant resistance to β -lactams, is the norm among the *Bacteroides fragilis* group, other anaerobic gram-negative bacilli in the genera *Prevotella*, *Porphyromonas*, and *Fusobacterium* have increasingly become β -lactamase positive. β -Lactamase production also has been described for clostridia. Metronidazole resistance in organisms other than non-spore-forming gram-positive bacilli has been described elsewhere, as has clindamycin resistance in anaerobic gram-negative bacilli (1–5).

Quinolones such as ciprofloxacin, ofloxacin, fleroxacin, pefloxacin, enoxacin, and lomefloxacin are inactive or only marginally active against anaerobes (6–10, 16, 17). Newer quinolones with increased antianaerobic activities include (i) those with slightly increased activities (sparfloxacina, grepafloxacin, and levofloxacin) and (ii) those with significantly improved antianaerobic activities (trovafloxacin, cinafloxacin, moxifloxacin, and DU-6859a) (6–10, 16, 17).

Gatifloxacin (AM-1155, CG 5501) is a broad-spectrum quinolone which shares with sparfloxacina and grepafloxacin a methyl piperazinyl side chain at position 7 and a cyclopropyl substituent at position 1 (9, 11–13, 19, 21). The current study used standardized agar dilution methodology to examine the activities of gatifloxacin compared with those of ciprofloxacin, sparfloxacina, trovafloxacin, ampicillin, ampicillin-sulbactam, clindamycin, and metronidazole against 351 anaerobes.

All anaerobes were clinical strains isolated during the past 4 years identified by standard procedures (18) and kept frozen in 200 g of skim milk (dehydrated skim milk; Difco Laboratories, Detroit, Mich.) per liter at -70°C until use. Prior to testing, strains were subcultured three times onto enriched sheep blood agar plates. Gatifloxacin Susceptibility powder was obtained from Bristol-Myers Squibb Laboratories, Wallingford, Conn., and other drugs were obtained from their respective manufacturers. β -Lactamase testing was performed by the nitrocefin disk method (Cefinase; BBL Microbiology Systems, Cockeysville, Md.) (1, 2). Agar dilution susceptibility testing

was performed according to the latest method (approved but not yet published) recommended by the National Committee for Clinical Laboratory Standards (15), with brucella agar with 5% sterile defibrinated laked sheep blood for non-*B. fragilis* group strains; sulbactam was added to ampicillin at a fixed ratio of 1:2. All quality control gram-negative and -positive strains (15) recommended by the National Committee for Clinical Laboratory Standards were included with each run; in every case, results (where available) were in control.

Among anaerobic gram-negative bacilli, 86.3% of *B. fragilis* group isolates, 61.2% of *Prevotella-Porphyromonas* isolates, and 5.0% of fusobacteria produced β -lactamase. Results of MIC testing are presented in Table 1. Overall, MICs at which 50% of the isolates are inhibited (MIC₅₀s) and MIC₉₀s (in micrograms per milliliter) were as follows: gatifloxacin, 0.5 and 4; ciprofloxacin, 2 and 32; sparfloxacina, 2 and 8; trovafloxacin, 1 and 4; ampicillin, 1 and 64; ampicillin-sulbactam, 0.5 and 4; clindamycin, 0.125 and 8; and metronidazole, 1 and >16, respectively.

Gatifloxacin and trovafloxacin had the lowest MICs of all quinolones tested, followed by sparfloxacina and ciprofloxacin. MICs of the former two compounds were similar, with trovafloxacin MICs tending to be 1 or 2 dilutions lower than those of gatifloxacin. Gatifloxacin and trovafloxacin MICs were lower for non-*B. fragilis* group anaerobic gram-negative bacilli other than *Prevotella bivia* and *Fusobacterium varium* and for gram-positive anaerobes. One each of three strains (*Bacteroides thetaiotaomicron*, *F. varium*, and *Lactobacillus* spp.) yielded gatifloxacin and trovafloxacin MICs of >8 $\mu\text{g}/\text{ml}$.

Addition of sulbactam enhanced the activities of ampicillin against β -lactamase-producing anaerobic gram-negative bacilli. Although most strains tested were susceptible (MICs of ≤ 2 $\mu\text{g}/\text{ml}$) to clindamycin, resistance was seen in some members of most groups tested. With the exception of one strain of *Prevotella denticola* with a metronidazole MIC of 16 $\mu\text{g}/\text{ml}$, the only anaerobes resistant to metronidazole were the anaerobic gram-positive bacilli.

All strains with unexpectedly high gatifloxacin, trovafloxacin, and metronidazole MICs were tested three times; in each case, results were identical.

Kato and coworkers (13) reported in vitro activity of gatifloxacin against a wide range of anaerobes. MIC₉₀s of 3.13 to 6.25 $\mu\text{g}/\text{ml}$ were found for all members of the *B. fragilis* group. MIC₉₀s for *P. bivia* were 6.25 $\mu\text{g}/\text{ml}$. By comparison, gatifloxa-

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TABLE 1. MICs (micrograms per milliliter) of agents

Organism	MIC range	MIC ₅₀	MIC ₉₀	Organism	MIC range	MIC ₅₀	MIC ₉₀
<i>Bacteroides fragilis</i> (10/10) ^a				<i>Prevotella intermedia</i> (7/13)			
Gatifloxacin	0.5-1	1	1	Gatifloxacin	0.25-1	0.5	0.5
Ciprofloxacin	4-8	8	8	Ciprofloxacin	1-2	1	2
Sparfloxacin	1-2	1	2	Sparfloxacin	2-8	2	4
Trovafoxacin	0.125-0.5	0.5	0.5	Trovafoxacin	0.5-1	1	1
Ampicillin	8-128	64	128	Ampicillin	≤0.125-16	2	8
Ampicillin-sulbactam	2-8	2	4	Ampicillin-sulbactam	≤0.125-1	0.5	1
Clindamycin	0.25-4	1	2	Clindamycin	≤0.016-0.03	≤0.016	0.03
Metronidazole	1-2	1	1	Metronidazole	≤0.125-2	1	2
<i>Bacteroides thetaiotaomicron</i> (11/11)				<i>Prevotella melaninogenica</i> (8/11)			
Gatifloxacin	1->32	2	2	Gatifloxacin	0.5-2	2	2
Ciprofloxacin	8->32	32	32	Ciprofloxacin	2-8	2	8
Sparfloxacin	1->32	2	4	Sparfloxacin	2-8	4	4
Trovafoxacin	0.5-32	1	1	Trovafoxacin	1-4	2	2
Ampicillin	32->128	64	64	Ampicillin	≤0.125->128	2	64
Ampicillin-sulbactam	2-8	2	4	Ampicillin-sulbactam	≤0.125-4	0.5	2
Clindamycin	1->32	4	8	Clindamycin	≤0.016-0.03	0.03	0.03
Metronidazole	1-2	1	1	Metronidazole	0.5-1	1	1
<i>Bacteroides distasonis</i> (3/10)				<i>Prevotella corporis</i> (3/11)			
Gatifloxacin	1-4	1	4	Gatifloxacin	0.25-1	0.5	0.5
Ciprofloxacin	8->32	8	>32	Ciprofloxacin	0.5-2	2	2
Sparfloxacin	2-8	4	4	Sparfloxacin	1-8	4	8
Trovafoxacin	0.5-4	1	1	Trovafoxacin	0.5-2	1	1
Ampicillin	4->128	8	>128	Ampicillin	≤0.125-64	≤0.125	8
Ampicillin-sulbactam	4-16	8	16	Ampicillin-sulbactam	≤0.125-2	≤0.125	1
Clindamycin	1->32	8	16	Clindamycin	≤0.016-0.03	≤0.016	0.03
Metronidazole	1-2	1	2	Metronidazole	≤0.125-0.5	≤0.125	0.25
<i>Bacteroides vulgatus</i> (10/10)				Miscellaneous <i>Prevotella/Porphyromonas</i> ^c (11/18)			
Gatifloxacin	0.5-4	1	2	Gatifloxacin	0.125-4	0.5	4
Ciprofloxacin	8->32	32	32	Ciprofloxacin	1-16	2	8
Sparfloxacin	1-2	1	2	Sparfloxacin	0.5-8	4	4
Trovafoxacin	0.25-0.5	0.25	0.5	Trovafoxacin	0.125-2	1	2
Ampicillin	4->128	16	>128	Ampicillin	≤0.125->128	2	64
Ampicillin-sulbactam	1-16	2	8	Ampicillin-sulbactam	≤0.125-8	0.5	2
Clindamycin	≤0.016->32	0.5	>32	Clindamycin	≤0.016-4	≤0.016	0.03
Metronidazole	1-2	1	2	Metronidazole	≤0.125-16	1	4
<i>Bacteroides ovatus/uniformis</i> ^b (10/10)				<i>Prevotella/Porphyromonas</i> (63/103)			
Gatifloxacin	1-2	2	2	Gatifloxacin	0.125-8	1	4
Ciprofloxacin	8-32	16	32	Ciprofloxacin	0.5->32	4	32
Sparfloxacin	2-8	2	4	Sparfloxacin	0.5-16	4	8
Trovafoxacin	0.5-2	1	2	Trovafoxacin	0.125-4	2	4
Ampicillin	32->128	64	>128	Ampicillin	≤0.125->128	4	64
Ampicillin-sulbactam	1-16	2	8	Ampicillin-sulbactam	≤0.125-8	0.5	4
Clindamycin	0.03->32	2	>32	Clindamycin	≤0.016-4	0.03	0.03
Metronidazole	0.25-2	1	2	Metronidazole	≤0.125-16	2	4
<i>Bacteroides fragilis</i> group (44/51)				<i>Fusobacterium nucleatum</i> (2/10)			
Gatifloxacin	0.5->32	1	2	Gatifloxacin	0.25-0.5	0.5	0.5
Ciprofloxacin	4->32	16	32	Ciprofloxacin	2-4	4	4
Sparfloxacin	1->32	2	4	Sparfloxacin	0.5-2	1	2
Trovafoxacin	0.125-32	0.5	1	Trovafoxacin	0.25-1	0.5	1
Ampicillin	4->128	32	>128	Ampicillin	≤0.125->128	0.5	>128
Ampicillin-sulbactam	1-16	2	8	Ampicillin-sulbactam	≤0.125->128	0.5	32
Clindamycin	≤0.016->32	2	>32	Clindamycin	0.06-0.125	0.06	0.125
Metronidazole	0.25-2	1	2	Metronidazole	≤0.125-0.5	≤0.125	0.25
<i>Prevotella bivia</i> (28/40)				<i>Fusobacterium necrophorum</i> (0/10)			
Gatifloxacin	2-8	4	8	Gatifloxacin	0.5-1	0.5	1
Ciprofloxacin	8->32	32	32	Ciprofloxacin	2-4	2	2
Sparfloxacin	4-16	8	8	Sparfloxacin	1-4	2	4
Trovafoxacin	2-4	2	4	Trovafoxacin	0.25-1	0.5	0.5
Ampicillin	≤0.125->128	4	64	Ampicillin	≤0.125	≤0.125	≤0.125
Ampicillin-sulbactam	≤0.125-8	1	4	Ampicillin-sulbactam	≤0.125	≤0.125	≤0.125
Clindamycin	≤0.016-0.125	0.03	0.06	Clindamycin	≤0.016-0.06	0.06	0.06
Metronidazole	1-8	4	4	Metronidazole	≤0.125-0.5	≤0.125	0.25
<i>Prevotella buccae</i> (6/10)				<i>Fusobacterium mortiferum</i> (0/10)			
Gatifloxacin	0.25-0.5	0.5	0.5	Gatifloxacin	0.25-0.5	0.5	0.5
Ciprofloxacin	2-4	2	2	Ciprofloxacin	2	2	2
Sparfloxacin	1-4	2	4	Sparfloxacin	1-2	1	2
Trovafoxacin	1-2	1	2	Trovafoxacin	1-2	1	2
Ampicillin	0.25->128	32	>128	Ampicillin	1->128	2	>128
Ampicillin-sulbactam	0.25-4	2	4	Ampicillin-sulbactam	1->128	2	128
Clindamycin	≤0.016-0.03	0.03	0.03	Clindamycin	0.06-0.125	0.125	0.125
Metronidazole	1-4	1	2	Metronidazole	≤0.125-0.5	0.25	0.25

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TABLE 1—Continued

Organism	MIC range	MIC ₅₀	MIC ₉₀
<i>Fusobacterium varium</i> (0/10)			
Gatifloxacin	2->32	4	4
Ciprofloxacin	4-32	8	8
Sparfloxacin	8->32	8	16
Trovafoxacin	4-16	4	8
Ampicillin	2-4	2	4
Ampicillin-sulbactam	1-4	2	2
Clindamycin	2-32	8	32
Metronidazole	≤0.125-0.5	0.25	0.5
Fusobacteria (2/40)			
Gatifloxacin	0.25->32	0.5	4
Ciprofloxacin	2-32	2	8
Sparfloxacin	0.5->32	2	8
Trovafoxacin	0.25-16	1	4
Ampicillin	≤0.125->128	2	128
Ampicillin-sulbactam	≤0.125->128	2	16
Clindamycin	≤0.016-32	0.125	16
Metronidazole	≤0.125-0.5	0.25	0.25
Peptostreptococci (0/55) ^d			
Gatifloxacin	0.06-1	0.5	1
Ciprofloxacin	0.25-4	1	4
Sparfloxacin	0.06-2	0.5	1
Trovafoxacin	0.06-1	0.25	0.5
Ampicillin	≤0.125-32	0.25	16
Ampicillin-sulbactam	≤0.125-32	0.25	16
Clindamycin	≤0.016->32	0.5	4
Metronidazole	≤0.125-2	1	2
Propionibacteria (0/19) ^e			
Gatifloxacin	0.25-0.5	0.5	0.5
Ciprofloxacin	0.5-1	1	1
Sparfloxacin	0.25-0.5	0.5	0.5
Trovafoxacin	1-2	1	1
Ampicillin	≤0.125-1	≤0.125	0.5
Ampicillin-sulbactam	≤0.125-1	≤0.125	0.5
Clindamycin	0.06-0.5	0.06	0.25
Metronidazole	>16	>16	>16
Other gram-positive non-spore-forming bacilli (0/28) ^f			
Gatifloxacin	0.25-16	1	2
Ciprofloxacin	1->32	4	32
Sparfloxacin	0.25-32	2	8
Trovafoxacin	0.125-8	1	2
Ampicillin	≤0.125-4	0.5	2
Ampicillin-sulbactam	≤0.125-2	0.5	2
Clindamycin	≤0.016-8	0.25	4
Metronidazole	0.25->16	>16	>16
<i>Clostridium perfringens</i> (0/20)			
Gatifloxacin	0.25-1	0.5	1
Ciprofloxacin	0.25-2	1	1
Sparfloxacin	0.125-1	0.5	1
Trovafoxacin	0.125-0.25	0.25	0.25
Ampicillin	≤0.125-0.5	≤0.125	0.25
Ampicillin-sulbactam	≤0.125-0.25	≤0.125	0.25
Clindamycin	0.03-4	1	4
Metronidazole	≤0.125-2	0.5	1
<i>Clostridium difficile</i> (0/10)			
Gatifloxacin	1-2	2	2
Ciprofloxacin	8-32	16	16
Sparfloxacin	4-8	8	8
Trovafoxacin	1-2	1	2
Ampicillin	1-8	2	2
Ampicillin-sulbactam	1-4	1	2
Clindamycin	4->32	16	>32
Metronidazole	≤0.125-0.25	0.25	0.25
Miscellaneous clostridia (0/25) ^g			
Gatifloxacin	0.125-2	0.5	2
Ciprofloxacin	0.5-8	2	8
Sparfloxacin	0.25-16	1	16
Trovafoxacin	0.125-2	0.5	2
Ampicillin	≤0.125-2	0.5	1
Ampicillin-sulbactam	≤0.125-2	0.5	1
Clindamycin	0.03-32	1	16
Metronidazole	≤0.125-1	0.25	1

Continued

TABLE 1—Continued

Organism	MIC range	MIC ₅₀	MIC ₉₀
All strains (109/351)			
Gatifloxacin	0.06->32	0.5	4
Ciprofloxacin	0.25->32	2	32
Sparfloxacin	0.06->32	2	8
Trovafoxacin	0.06-32	1	4
Ampicillin	≤0.125->128	1	64
Ampicillin-sulbactam	≤0.125->128	0.5	4
Clindamycin	≤0.016->32	0.125	8
Metronidazole	≤0.125->16	1	>16

^a Number of strains β-lactamase positive/number of strains tested.^b *Bacteroides ovatus*, 5; *Bacteroides uniformis*, 5.^c *Prevotella oralis*, 1; *Prevotella oris*, 2; *Prevotella denticola*, 1; *Prevotella disiens*, 8; *Prevotella* spp., 2; *Porphyromonas asaccharolytica*, 3; *Porphyromonas gingivalis*, 1.^d *Peptostreptococcus asaccharolyticus*, 14; *Peptostreptococcus magnus*, 13; *Peptostreptococcus anaerobius*, 14; *Peptostreptococcus tetradius*, 14.^e *Propionibacterium acnes*, 18; *Propionibacterium* spp., 1.^f *Actinomyces* spp., 6; *Eubacterium* spp., 6; *Bifidobacterium* spp., 4; *Lactobacillus* spp., 12.^g *Clostridium tertium*, 5; *Clostridium bifementans*, 4; *Clostridium cadaveris*, 2; *Clostridium sordelli*, 5; *Clostridium histolyticum*, 1; *Clostridium* spp., 8.

cin was more active against *Prevotella intermedia*, *Porphyromonas gingivalis*, *Fusobacterium* species, peptostreptococci, and *Clostridium perfringens*, with MIC₉₀s of ≤0.39 μg/ml for all species except *Peptostreptococcus asaccharolyticus*. Gatifloxacin was not active against *Clostridium difficile* (MIC₉₀ of 25 μg/ml) (13). Gatifloxacin MICs were several dilutions lower than those of ciprofloxacin, ofloxacin, tosufloxacin, temafloxacin, and sparfloxacin (13). By contrast, Bauernfeind (9), in a preliminary study, has reported a MIC₉₀ of 2 μg/ml for *C. difficile*.

In general, our results with gatifloxacin are similar to those reported by Kato et al. (13) and Bauernfeind (9). However, in contrast to findings by Kato et al. (13), we found lower gatifloxacin MICs, similar to those reported by Bauernfeind (9) against *C. difficile*. Although Kato et al. (13) found MIC₉₀s of 0.39 μg/ml against 13 fusobacteria, the species of these strains was not reported. Wexler and coworkers (20) have reported elevated trovafoxacin MICs against *F. varium* compared to those of the same drug against other fusobacteria, and it is probable that the same applies for gatifloxacin. This needs to be confirmed by others.

Antianaerobic activities of ciprofloxacin, sparfloxacin, and trovafoxacin are similar to those reported previously (7-10, 16, 17, 20). Slightly higher trovafoxacin MICs obtained in this study may be dependent on the composition of strains tested compared to those in other reports by us and others (16, 20). Activities of ampicillin-sulbactam, clindamycin, and metronidazole reflect well-known patterns obtained with these drugs, with ampicillin-sulbactam being very active against β-lactamase-producing strains, clindamycin being active against all strains except some clostridia (especially *C. difficile*), and metronidazole being active against all strains except anaerobic gram-positive bacilli. High β-lactam MICs for β-lactamase-negative fusobacteria have been described before (1-5). We do not have an explanation for the metronidazole resistance encountered in one strain of *P. denticola*; this phenomenon is currently under investigation.

Nakashima and coworkers (14) have reported maximum concentrations of drug in serum in healthy human volunteers of 0.873, 1.71, 3.35, and 5.41 μg/ml after single oral doses of 100, 200, 400, and 600 mg, respectively. Values for area under the concentration-time curve after the four doses were 7.0, 14.5, 32.4, and 53.5 μg · h/ml, respectively. Serum concentrations reached a peak between 1 and 2 h (14). With the above

pharmacokinetic data considered with the MIC data presented above as well as its known activity against members of the family *Enterobacteriaceae* (9, 11, 12, 21), gatifloxacin shows promise in treatment of mixed anaerobic infections, especially of those of the respiratory tract, ear, nose and throat, skin and soft tissue, and bite wounds. Clinical studies will be necessary to validate these hypotheses.

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