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In Vitro Activities of Gatifloxacin, Two Other Quinolones, and Five Nonquinolone Antimicrobials against Obligately Anaerobic Bacteria

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The activity of the new fluoroquinolone gatifloxacin was compared with those of other quinolones and antimicrobial agents of other classes against 294 anaerobes by the broth microdilution technique. For all strains tested, gatifloxacin MICs at which 50 and 90% of the isolates were inhibited were 0.5 and 2 mg/liter, respectively, and were 3 to 4 dilution steps lower than, e.g., ciprofloxacin.

Gatifloxacin (AM-1155) is a new fluoroquinolone with a 3-methylpiperazine at position 7 of the quinolone ring and a methoxy group at position 8. It is available orally. Gatifloxacin has a broad spectrum against gram-positive and gram-negative bacteria and is also effective against *Mycoplasma* spp., *Chlamydia* spp., and mycobacteria (2, 8–10, 14, 19–21, 25). In a study encompassing 404 anaerobic strains from Japan, the results for gatifloxacin were described as "mediocre" (11). While this study was under revision, two other articles were published: Ednie et al. showed similar MICs of gatifloxacin and trovafloxacin by testing 351 strains of anaerobes (5), while Goldstein et al. tested the in vitro activities of gatifloxacin against 420 bite wound isolates, including 112 anaerobes. Gatifloxacin was active against all aerobes tested and against *Bacteroides tectum*, *Prevotella* spp., *Porphyromonas* spp., and peptostreptococci. Fusobacteria were sometimes resistant (7).

We compared the in vitro activities of gatifloxacin (Grünenthal GmbH, Aachen, Germany) to those of trovafloxacin (Pfizer International Pharmaceuticals Group, New York, N.Y.), ciprofloxacin (Bayer AG, Leverkusen, Germany), metronidazole (Bayer AG), clindamycin (Sigma Chemical Co., St. Louis, Mo.), imipenem (Merck & Co., Inc., West Point, N.Y.), amoxicillin-clavulanate (10:1) (SmithKline Beecham Pharma GmbH, Munich, Germany), and erythromycin (Serva Feinbiochemica GmbH & Co., Heidelberg, Germany) against 294 strains of obligately anaerobic bacteria isolated from clinical specimens either in Germany or in California. The species and numbers of isolates tested are shown in Table 1. All strains were identified as detailed previously by Claros et al. (3, 4).

MICs were determined by the broth microdilution technique with 96-well microdilution plates (Greiner GmbH, Frickenhausen, Germany). The plates were filled semiautomatically (Quick Spense; Sandy Spring Instrument Company, Inc., Germantown, Md.) with 100 μl of Wilkins-Chalgren anaerobe broth (Oxoid Unipath Ltd., Basingstoke, United Kingdom) containing the final antibiotic concentrations. The plates were stored at −80°C until use. For this study, the plates were thawed in an anaerobic chamber (WA 6200; Heraeus Instruments, Hanau, Germany) containing an atmosphere of 80% N_2, 15% CO_2, and 5% H_2. Then, the bacteria were delivered by a semiautomated inoculator (MIC-2000; Dynatech Laboratories, Inc., Chantilly, Va.). The final inoculum was approximately 1.0×10^5 CFU/well. Incubation was usually for 48 h (96 h for *Bilophila wadsworthia*) at 37°C in the anaerobic chamber. The MIC was defined as the lowest antibiotic concentration that inhibited visible growth.

Bacteroides fragilis ATCC 25285, *B. fragilis* ATCC 23745, *Bacteroides ovatus* ATCC 8483, *Bacteroides vulgatus* ATCC 8482, *Bacteroides thetaiotaomicron* ATCC 29148, *Bacteroides caccae* ATCC 43185, *Fusobacterium mortiferum* ATCC 9817, *Fusobacterium varium* ATCC 8501, and *Peptostreptococcus magnus* ATCC 14955 were used as reference strains. The MICs showed conformity with published results of the National Committee for Clinical Laboratory Standards and the German standard-setting organization Deutsches Institut für Normung (13, 15).

MIC distributions and MICs at which 50 or 90% of the isolates were inhibited (MIC_{50} and MIC_{90}, respectively) for gatifloxacin, other quinolones, and nonquinolone antimicrobials are given in Table 1. In addition, in Table 2 the results are shown as cumulative percentages of strains inhibited at a given MIC. Overall, the MIC_{50} and MIC_{90} (in milligrams per liter), respectively, for all strains were as follows: imipenem, metronidazol, and trovafloxacin, 0.25 and 1; gatifloxacin, 0.5 and 2; clindamycin, 0.5 and 4; amoxicillin-clavulanate, 1 and 4; ciprofloxacin, 4 and 32; erythromycin, 4 and >32. At a breakpoint concentration of ≤1 mg of gatifloxacin per liter, 83% of all strains tested, 90% of the *B. fragilis* strains, and 81% of all *Bacteroides* spp. were inhibited. The MIC_{50} and MIC_{90} of gatifloxacin were 1 dilution step higher than those of trovafloxacin with respect to all strains tested. In contrast, gatifloxacin MIC_{50} and MIC_{90} were 3 to 4 dilution steps lower than those of ciprofloxacin. Gatifloxacin and trovafloxacin MICs were significantly lower for anaerobic gram-negative bacilli other than fusobacteria and *Bilophila wadsworthia* than MICs of ciprofloxacin. For *Clostridium* spp., no major disparities were found between gatifloxacin, trovafloxacin, and ciprofloxacin MIC_{50}, whereas the MIC_{90} for ciprofloxacin was 3 dilution steps higher than those of gatifloxacin and trovafloxacin.

In comparison with other studies (1, 5, 6, 12, 16–18, 22–24), we found similar MIC_{50} and MIC_{90} of trovafloxacin, ciprofloxacin, metronidazole, clindamycin, imipenem, erythromycin, and amoxicillin-clavulanate. Like Pankuch et al. (16), we found

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TABLE 1. In vitro activities of gatifloxacin and other antimicrobial agents against anaerobic bacteria

Organism (no. of isolates)	Antimicrobial agent	No. of isolates inhibited at MIC (mg/liter) of:												MIC_{50}	MIC_{90}
		≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32		
B. fragilis (62)	Gatifloxacin		2	4	28	17	5	2	2	1			1	0.25	1
	Ciprofloxacin			2	4	1		4	32	8	4	3	4	4	32
	Trovafloxacin		5	37	12	3	1	3	1					0.125	0.5
	Clindamycin	3	1	6	10	13	13	5	5	4			2	0.5	4
	Metronidazole			5	21	26	10							0.5	1
	Imipenem	1	21	15	15	9	1							0.125	0.5
	Amoxicillin-clavulanate				2	13	37	4	4	1		1		1	2
	Erythromycin					1	15	13	16	8	3	1	5	4	16
B. ovatus (70)	Gatifloxacin		1		2	8	34	15	2	4	3		1	1	8
	Ciprofloxacin			1	1		1		3	11	39	4	10	16	>32
	Trovafloxacin	1	1	1	28	30	6	2	1					0.5	1
	Clindamycin	4	1	3	5	11	19	10	8	2	1		6	1	8
	Metronidazole		3	7	17	30	12	1						0.5	1
	Imipenem	1	4	20	29	7	7	2						0.25	1
	Amoxicillin-clavulanate		1		2	5	30	14	9	1	3	4	1	1	16
	Erythromycin				2	2	4	9	25	9	4	1	14	4	>32
B. vulgatus (29)	Gatifloxacin		1	10	4	7	4	1		1	1			0.25	1
	Ciprofloxacin				10	2			2	5	5	4	1	8	32
	Trovafloxacin		6	15	4	2		1	1					0.125	0.5
	Clindamycin	2			4	5	9	4	4	1				1	4
	Metronidazole		1	5	13	8	2							0.25	0.5
	Imipenem	1	4	2	8	12	2							0.25	0.5
	Amoxicillin-clavulanate				5	11	2	4	4	2	1			0.5	4
	Erythromycin					1	15	8	1	2	2			1	8
B. thetaiotaomicron (17)	Gatifloxacin		3	1	1		10	2						1	1
	Ciprofloxacin			4					2	2	8		1	16	16
	Trovafloxacin			4	6	6	1							0.25	0.5
	Clindamycin	1		3	1	1	2	4	3				2	2	4
	Metronidazole	1	1	4		6	5							0.5	1
	Imipenem		4	6	5	2								0.125	0.25
	Amoxicillin-clavulanate				1	3	9		1	2		1		1	8
	Erythromycin						6	2	1	5	1	1	1	4	16
B. caccae (11)	Gatifloxacin		3			1	5	1	1					1	2
	Ciprofloxacin			2	1					2	4	1	1	16	32
	Trovafloxacin		2		6	3								0.25	0.5
	Clindamycin				2	1	2	1	1			1	3	2	>32
	Metronidazole			2	2	7								0.5	0.5
	Imipenem			3	3	5								0.25	0.5
	Amoxicillin-clavulanate					1	3	2	4	1				2	4
	Erythromycin						1	2	1	3			4	8	>32
B. distasonis (8)	Gatifloxacin				2	3	3								
	Ciprofloxacin								2	3	3				
	Trovafloxacin				8										
	Clindamycin				1	1	1	2		2			1		
	Metronidazole		1		2	4	1								
	Imipenem			2	1	1	4								
	Amoxicillin-clavulanate					1	2	2	2			1			
	Erythromycin						1	1		3	1		2		
Prevotella spp.[a] (11)	Gatifloxacin			1	6		1	2	1					0.25	2
	Ciprofloxacin				1	1	5				3	1		1	16
	Trovafloxacin			1	2	5	2	1						0.5	1
	Clindamycin	7		1	1	1			1					≤0.03	0.5
	Metronidazole			2	4	2	3							0.25	1
	Imipenem	2	6	1	1		1							0.06	0.25
	Amoxicillin-clavulanate		3		2	2	2	1		1				0.5	2
	Erythromycin			1		2	5	2		1				1	2
Fusobacterium spp.[b] (17)	Gatifloxacin		1		3	2	3	5		3				1	8
	Ciprofloxacin			1		1	5	1	1	5	1		2	4	16
	Trovafloxacin		2			2	8	5						1	2

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TABLE 1—*Continued*

Organism (no. of isolates)	Antimicrobial agent	No. of isolates inhibited at MIC (mg/liter) of:											MIC_{50}	MIC_{90}
		≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32	
	Clindamycin		1	2		2	3	4	1		1		3	2	>32
	Metronidazole		1	5	7	2	2							0.25	0.5
	Imipenem		2	1	3	3	6	1	1					0.5	1
	Amoxicillin-clavulanate				3	3	5	3	3					1	4
	Erythromycin					2	2	1	1	1	1		9	>32	>32
B. wadsworthia (31)	Gatifloxacin				8	20	3							0.5	0.5
	Ciprofloxacin			12	8	5	2	1	2	1				0.25	2
	Trovafloxacin			3	1	9	18							1	1
	Clindamycin			4	11	14	2							0.5	0.5
	Metronidazole	18	5	4	3	1								≤0.03	0.25
	Imipenem		2	1	5	20	3							0.5	0.5
	Amoxicillin-clavulanate					1	8	17	3	2				2	4
	Erythromycin						3	2	2	14	9	1		8	16
Clostridium spp.[c] (29)	Gatifloxacin		8	4	7	4	6							0.25	1
	Ciprofloxacin		3	8	5	1	1	1	4	6				0.25	8
	Trovafloxacin	5	7	6	5	2	4							0.125	1
	Clindamycin	2	1	4	2	10	5	2	1		1	1		0.5	2
	Metronidazole		4	7	8	7	3							0.25	0.5
	Imipenem		9	8	7	1	4							0.125	1
	Amoxicillin-clavulanate		6	10	7	3	3							0.125	0.5
	Erythromycin				2	7	11	5	3	1				1	4
Peptostreptococcus spp.[d] (9)	Gatifloxacin		1	5	2	1									
	Ciprofloxacin		2	3		2	1		1						
	Trovafloxacin	1	4	3	1										
	Clindamycin	1		4		1	2	1							
	Metronidazole		3	3		3									
	Imipenem	1	4	3		1									
	Amoxicillin-clavulanate	1	3	3		1	1								
	Erythromycin		1	1		1	1	1	1	2	1				

[a] *P. buccalis* (3), *P. denticola* (2), *P. disiens* (1), *P. intermedia* (2), and *P. oralis* (3).
[b] *F. mortiferum* (6), *F. naviforme* (1), *F. necrogenes* (1), *F. necrophorum* (2), *F. russii* (2), and *F. varium* (5).
[c] *C. bifermentans* (2), *C. cadaveris* (2), *C. clostridioforme* (4), *C. difficile* (6), *C. glycolicum* (1), *C. innocuum* (2), *C. paraputrificum* (1), *C. perfringens* (5), *C. ramosum* (3), *C. sporogenes* (1), *C. subterminale* (1), and *C. tertium* (1).
[d] *P. anaerobius* (2), *P. asaccharolyticus* (2), and *P. magnus* (5).

a moderate level of clindamycin resistance for all strains tested (MICs for 10% of the strains were >4 mg/liter).

In general, our MICs of gatifloxacin against anaerobes have confirmed and extended the findings of previous reports (2, 5, 7, 9, 11, 21, 25). However, in contrast to the report of Wakabayashi et al., who tested 70 Japanese isolates, we found lower MIC_{50} and MIC_{90} of gatifloxacin against *B. fragilis* (21). Likewise, Kato et al. found higher MIC_{50} and MIC_{90} of gatifloxacin for *B. fragilis* and *B. thetaiotaomicron* by testing 404 Japanese isolates of anaerobic bacteria (11). Of the *B. fragilis* strains tested, only 76 and 83% were inhibited at concentrations of 0.78 and 1.56 mg of gatifloxacin per liter, respectively, whereas in our study, 90% of *B. fragilis* strains were inhibited at 1 mg/liter. However, our results for *Bacteroides* spp. are similar to those published by Ednie et al. (5). Moreover, in accordance with the results of Ednie et al., we found similar gatifloxacin MIC_{50} and MIC_{90} for fusobacteria, whereas Goldstein and coworkers found higher values and Kato et al. found lower values (5, 7, 11). In contrast to the findings of Ednie et al. and Goldstein et al., we found lower MIC_{90} for peptostreptococci

TABLE 2. Cumulative percentages of strains (n = 294) inhibited at given MICs

Antimicrobial agent	% of strains inhibited at MIC (mg/liter) of:											
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32
Gatifloxacin	0	7	15	37	58	83	93	95	98	99	99	100
Ciprofloxacin	0	2	13	23	28	33	35	52	66	89	94	100
Trovafloxacin	2	12	35	60	81	95	99	100				
Clindamycin	7	8	17	30	50	70	81	90	93	94	94	100
Metronidazole	7	13	28	54	87	100	100					
Imipenem	2	21	42	68	89	99	100	100				
Amoxicillin-Clavulanate	0	5	9	17	32	66	82	93	96	97	100	100
Erythromycin	0	0	1	2	8	30	45	63	79	87	88	100

(5, 7). The disparities might be due to technical differences, i.e., different media and our use of the broth microdilution technique rather than the agar dilution method.

It is recognized that the results of in vitro anaerobe susceptibility testing do not always correlate with in vivo findings. Although Kato et al. described "mediocre" in vitro activity of gatifloxacin against *B. fragilis*, they reported that gatifloxacin was effective against both *B. fragilis* and *Escherichia coli* in a mixed infection in a rat granuloma pouch in vivo (11). Hence, clinical studies are required to determine the roles of gatifloxacin in mixed and anaerobic infections.

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