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Comparative In Vitro Activities of Gemifloxacin, Other Quinolones, and Nonquinolone Antimicrobials against Obligately Anaerobic Bacteria

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The in vitro activity of gemifloxacin was compared to that of other quinolone and nonquinolone antimicrobials against 204 anaerobes by the agar dilution technique. The data indicate that gemifloxacin has a rather selective anaerobic activity. Most *Peptostreptococcus, Porphyromonas*, and *Fusobacterium* species are susceptible, while gemifloxacin's activity against other gram-negative anaerobes appears to be variable.

Gemifloxacin mesylate (SB 265805) is a fluoroquinolone with a novel oxime-derivatized pyrrolidine substituent at position C7 which is thought to confer the enhanced activity against gram-positive bacteria (11). A limited number of studies have focused on its potential activity against anaerobic bacteria, demonstrating variable susceptibility patterns of the different anaerobic genera (3, 4, 7–10, 12). To further evaluate its utility in the treatment of infections involving anaerobes, we studied the in vitro activity of gemifloxacin and several comparator antimicrobials against selected anaerobic isolates from clinical specimens obtained in Germany.

The 204 anaerobic strains used in this study were recent clinical isolates (collected from September 1997 through March 2000) from our institute, the Department of Medical Microbiology of the University of Tübingen, Tübingen, Germany, and the Institute of Medical Microbiology of the University of Halle, Halle, Germany. The numbers and species of isolates tested are given in Table 1. The bacterial strains were identified by use of prereduced anaerobically sterilized (PRAS) biochemicals (Carr Scarborough Microbiologicals, Stone Mountain, Ga.) to test for fermentation of arabinose, rhamnose, trehalose, salicin, sucrose, and xylan; hydrolysis of esculin; and production of indole. Bile resistance was determined by growth in PRAS peptone-yeast broth containing 20% bile. Identification schemes were followed as detailed previously by Claros et al. (1, 2). In addition, RapID ANA II (Innovative Diagnostic Systems, Norcross, Ga.) and, in some cases, ATB 32A (bioMérieux, Marcy l'Etoile, France) were inoculated, and the results were interpreted according to the manufacturer's instructions.

Susceptibilities were determined by an agar dilution method according to the National Committee for Clinical Laboratory Standards (NCCLS) using brucella agar (Difco Laboratories, Detroit, Mich.) supplemented with hemin of 5 μg/ml, vitamin K at 1 μg/ml, and 5% laked horse blood (Oxoid GmbH, Wesel, Germany) (13). Serial doubling dilutions (0.03 to 32 mg/liter) were prepared for all compounds tested. Dilutions of the antibiotics were made according to standard procedures on the day of the test. Inocula were prepared according to NCCLS standards (13). The final inoculum density was calculated to be approximately 10^5 CFU/spot. The individual inocula were applied by use of a semiautomatic replicator device (A400 Multipoint Inoculator; Bachhofer GmbH, Reutlingen, Germany). The MICs were determined after incubation in an anaerobic chamber (WA 6600; Heraeus Instruments, Hanau, Germany) containing an atmosphere of 80% N_2, 15% CO_2, and 5% H_2 for 48 h at 37°C. *Bacteroides fragilis* ATCC 25285 and *Bacteroides thetaiotaomicron* ATCC 29741 served as controls to monitor the stability of the antimicrobial preparations. Antimicrobial reference powders were as follows: gemifloxacin and amoxicillin-clavulanate (2:1) (SmithKline Beecham Pharma GmbH, Munich, Germany); moxifloxacin (Bayer, Leverkusen, Germany); penicillin G (Serva, Heidelberg, Germany); imipenem (MSD, Haar, Germany); and clindamycin and metronidazole (Sigma, Steinheim, Germany).

The MIC_{90}s of gemifloxacin were equal to or one to two dilutions lower than those of moxifloxacin against various species of *Peptostreptococcus*. The MIC_{90}s for *Peptostreptococcus asacharolyticus, P. micros*, and *P. prevotii* were between 0.125 and 0.25 mg/liter. However, some isolates of *P. anaerobius* and *P. magnus* were resistant, resulting in gemifloxacin MIC_{90}s of 0.5 and 4 mg/liter, respectively, indicating that the activity of gemifloxacin is not entirely predictable, even against gram-positive anaerobes, and that there is species variability in its activity against peptostreptoccoci. Goldstein et al. (8) noted far lower MIC_{90}s for these species (0.03 and 0.06 mg/liter, respectively). Interestingly, the MIC ranges at least of *P. anaerobius* indicate that Goldstein similarly found isolates for which the MICs were up to 8 mg/liter, so that the differences may be explained by the significantly smaller number of isolates tested in Goldstein's study (13 versus 23 and 14 versus 24 isolates of *P. anaerobius* and *P. magnus*, respectively). Differences in local susceptibility patterns may further contribute to the discrepancies.

Gemifloxacin was active against *B. fragilis* at ≤4 mg/liter with an MIC range of 0.5 to 4 mg/liter. Similar results were reported by Goldstein et al. (8), who found an MIC_{90} of 2 mg/liter and

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TABLE 1. In vitro activity of gemifloxacin and other quinolone and non-quinolone antimicrobials against obligately anaerobic bacteria

Organism (no. of isolates) and antimicrobial agent	No. of isolates for which the MIC (mg/liter) was:												MIC (mg/liter)	
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Bacteroides fragilis (26)														
Gemifloxacin					5	17	1	3					1	4
Moxifloxacin				5	15	4	2						0.5	1
Penicillin G										5	20	1	32	32
Amoxicillin-clavulanate			8	15	1	2							0.25	0.5
Imipenem	6	17	3										0.06	0.125
Metronidazole					9	14	3						1	2
Clindamycin		1	1	1	12	5				1	5		0.5	32
Fusobacterium spp. (24)														
Gemifloxacin	1	1	4	8	8	2							0.25	0.5
Moxifloxacin			4	6	3	5	4		2				0.5	2
Penicillin G	11	3	3	2	2			1			1	1	0.06	4
Amoxicillin-clavulanate	20			2	1		1						≤0.03	0.25
Imipenem	7	10	3	1	3								0.06	0.5
Metronidazole	1	3	7	5	4		2					2	0.25	2
Clindamycin	14	4	2	1		2		1					≤0.03	1
Peptostreptococcus anaerobius (23)														
Gemifloxacin	1		17	2	1		1		1				0.125	0.5
Moxifloxacin		1	15	3	1	1	1	1					0.125	1
Penicillin G		1	1	16	4			1					0.25	0.5
Amoxicillin-clavulanate	2	1	3	11	5	1							0.25	0.5
Imipenem	23												≤0.03	≤0.03
Metronidazole			1	5	12	1	3				1		0.5	2
Clindamycin	6	7	7	1	2								0.06	0.25
Peptostreptococcus asaccharolyticus (22)														
Gemifloxacin	3	2	11	4	2								0.125	0.25
Moxifloxacin			2	6	9	1	3	1					0.5	2
Penicillin G	11		4	3	2	2							0.03	1
Amoxicillin-clavulanate	13	1	3	4	1								0.03	0.25
Imipenem	13	4	2	2	1								0.03	0.25
Metronidazole		1	2	4	6	9							1	2
Clindamycin	2	6	9	2		1						2	0.12	1
Peptostreptococcus magnus (24)														
Gemifloxacin	5	12	1			3		1	1	1			0.06	4
Moxifloxacin		2	8	7	2	1		1	1	1	1		0.25	4
Penicillin G		2	4	13	4			1					0.25	0.5
Amoxicillin-clavulanate		2	5	12	5								0.25	5
Imipenem		7	8	8	1								0.125	0.25
Metronidazole			1	5	8	8	2						0.5	1
Clindamycin		3	7	5	5	1	1					2	0.25	2
Peptostreptococcus micros (24)														
Gemifloxacin	6	1	17										0.125	0.125
Moxifloxacin	1		1	22									0.25	0.25
Penicillin G	21	2		1									≤0.03	0.06
Amoxicillin-clavulanate	21	1		2									≤0.03	0.06
Imipenem	3	19	2										0.06	0.06
Metronidazole	7	5	3	7	2								0.125	0.25
Clindamycin	1		3	13	6			1					0.25	0.5
Peptostreptococcus prevotii (20)														
Gemifloxacin	7	7	4	2									0.06	0.125
Moxifloxacin			1	9		1	7	1		1			0.25	2
Penicillin G		5	11	3	1								0.125	0.25
Amoxicillin-clavulanate	13		1	6									≤0.03	0.25
Imipenem	13	3	4										≤0.03	0.125
Metronidazole			7	1	3	8	1						0.5	1
Clindamycin	4	6	2	3		3	1				1		0.06	1
Porphyromonas[b] spp. (20)														
Gemifloxacin	9	4	7										0.06	0.125
Moxifloxacin	18	2											≤0.03	≤0.03
Penicillin G	20												≤0.03	≤0.03

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TABLE 1—*Continued*

Organism (no. of isolates) and antimicrobial agent	No. of isolates for which the MIC (mg/liter) was:												MIC (mg/liter)	
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32	MIC_{50}	MIC_{90}
Amoxicillin-clavulanate	20												≤0.03	≤0.03
Imipenem	20												≤0.03	≤0.03
Metronidazole	20												≤0.03	≤0.03
Clindamycin	20												≤0.03	≤0.03
Prevotella[c] spp (21)														
Gemifloxacin	1			2	2	13	2		1				1	2
Moxifloxacin	1			2	12	4	2						0.5	1
Penicillin G	1	2	10	1			1	3	1			2	0.125	8
Amoxicillin-clavulanate	9	8	2	2									0.06	0.125
Imipenem	18	3											≤0.03	0.06
Metronidazole		1		3	8	3	2	3			1		0.5	4
Clindamycin	20											1	0.015	0.03

[a] That is, *Fusobacterium necrophorum* (16), *F. nucleatum* (6), *F. mortiferum* (1), and *F. varium* (1).
[b] That is, *Porphyromonas gingivalis* (13), *P. endodontalis* (3), *P. asaccharolytica* (2), and *P. levii* (2).
[c] That is, *Prevotella melaninogenica* (10), *P. oris* (4), *P. intermedia* (3), *P. bivia* (1), *P. buccae* (1), *P. denticola* (1), and *P. disiens* (1).

a range of 0.5 to 2 mg/liter. Marco et al. (12), who tested 35 isolates of *B. fragilis*, reported an MIC range of 0.5 to 8 mg/liter and an MIC_{90} of 1 mg/liter. Wise and Andrews (14) originally proposed a gemifloxacin breakpoint of 0.5 mg/liter based on the formula of the British Society for Antimicrobial Chemotherapy. Recently, even more conservative criteria using a ≤0.25-mg/liter susceptible MIC breakpoint have been proposed (5). Yet, already with the previously proposed criteria, a large percentage of *B. fragilis* strains would be resistant.

As indicated by the wide range of MIC values, *Prevotella* spp. exhibited variable susceptibilities against gemifloxacin. Goldstein et al. (8) tested a large number of *Prevotella* isolates and reported marked differences between various *Prevotella* spp. Most of the isolates tested in our study were *Prevotella melaninogenica* and *P. intermedia*, corresponding to the more resistant species of the isolates tested by Goldstein et al. Therefore, discrepancies between the studies in the overall activity of gemifloxacin against *Prevotella* may be explained by the marked differences in susceptibility of the various species.

All *Porphyromonas* isolates tested, including strains of *Porphyromonas gingivalis* (13), *P. endodontalis* (3), *P. asaccharolytica* (2), and *P. levii* (2), were inhibited by ≤0.125 mg of gemifloxacin per liter.

Most of the fusobacteria in our study were also susceptible to gemifloxacin, with an MIC_{90} of 0.5 mg/liter. The activity of gemifloxacin against fusobacteria was one to two dilutions lower than that of moxifloxacin. The majority of strains included in our study were *Fusobacterium necrophorum* (16 of 24) and *F. nucleatum* (6 of 24). Goldstein et al. (9) reported similar MIC_{90} values for these species (0.5 and 0.25 mg/liter, respectively).

All anaerobes tested in this study were susceptible to the comparator antimicrobials imipenem and amoxicillin-clavulanate according to NCCLS criteria (13). For metronidazole and clindamycin, the overall susceptibility rates were 98 and 93%, respectively. As judged by the difference between penicillin and amoxicillin-clavulanate susceptibility, 26% of the isolates were lactamase producers.

In conclusion, the antimicrobial potency of gemifloxacin against anaerobic bacteria appears to be variable. In accordance with previously published studies, the majority of the *Peptostreptococcus* and *Porphyromonas* strains appear to be susceptible. Yet the present study shows that unequal susceptibilities between species of the same genus exist. Furthermore, possible variations between local susceptibility patterns must be taken into account when the use of gemifloxacin in treating anaerobic infections by these species is considered. Compared to the general resistance of fusobacteria toward the older quinolones (6), gemifloxacin clearly shows enhanced activity against these pathogens. Against other gram-negative anaerobes gemifloxacin exhibits only moderate activity. Considered in light of the complex nature of most anaerobic infections, the data presented here must be regarded as preliminary, and further clinical studies appear warranted to evaluate the role of gemifloxacin in such infections.

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