

In Vitro Activities of a New Des-Fluoro(6) Quinolone, Garenoxacin, against Clinical Anaerobic Bacteria

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The antimicrobial activities of garenoxacin and eight other antibiotics against 641 anaerobic isolates were evaluated with the NCCLS agar dilution method. Overall, the MICs of garenoxacin for 50 and 90% of the strains tested (in micrograms per milliliter) were as follows: *Bacteroides fragilis* group, 0.5 and 2; *Prevotella* spp., 0.25 and 2; *Fusobacterium* spp., 0.25 and 0.5; *Porphyromonas* spp., 0.125 and 0.25; *Bilophila wadsworthia*, 0.5 and 1; *Veillonella* spp., 0.25 and 0.5; *Clostridium* spp., 0.25 and 1; *Clostridium difficile*, 2 and >64; *Bifidobacterium* spp., 1 and 2; *Eggerthella lenta*, 0.25 and 1; *Propionibacterium* spp., 0.5 and 0.5; gram-positive cocci, 0.125 and 0.25.

Resistance to β -lactams, clindamycin, and metronidazole among anaerobes is increasing worldwide (5, 10, 16, 20, 21, 23). The older quinolones ciprofloxacin and levofloxacin provide only limited activity against many anaerobic species (7, 8, 11, 14, 28, 31). This deficiency has been addressed in the development of newer quinolones such as moxifloxacin or gatifloxacin with significantly improved antianaerobic activity (2, 4, 8, 11, 26, 31).

Garenoxacin is a novel orally and parenterally available des-fluoro(6) quinolone that lacks a fluorine molecule at the C-6 position. It displays a high degree of in vitro activity against a broad range of gram-positive and gram-negative bacterial pathogens, including anaerobes (6, 12, 13, 15, 17, 24, 25, 29, 30).

In this study, the antianaerobic activity of garenoxacin was compared to those of antianaerobic reference drugs and three other fluoroquinolones against 641 anaerobic bacteria isolated from human clinical sources (i.e., blood culture, peritonitis, chronic sinusitis and otitis, lung abscess) during the years 2000 and 2001 at the Department of Microbiology, Faculty of Pharmacy, University of Lille, Lille, France, or the Institute of Medical Microbiology and Epidemiology of Infectious Diseases, University of Leipzig, Leipzig, Germany. All bacteria were identified in accordance with classical methods (18), subcultured, and then frozen in Rosenow medium (Bio-Rad, Marnes-la-Coquette, France) or in skim milk (Oxoid, Basingstoke, Hampshire, England) at -70°C until use. Four American Type Culture Collection (ATCC) control strains suggested by the NCCLS (*Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *Clostridium perfringens* ATCC 13124, and *Eggerthella lenta* ATCC 43055) were included with each test run; in every case, results were within the control range.

The following antimicrobial agents were obtained as powders of known potency from their respective manufacturers: amoxicillin and clavulanic acid (SmithKline Beecham), imipenem (Merck Sharp & Dohme), clindamycin (Pharmacia),

metronidazole (Sigma), ciprofloxacin and moxifloxacin (Bayer), levofloxacin (Aventis), and garenoxacin (Bristol-Myers Squibb).

Agar dilution susceptibility testing was performed in accordance with NCCLS document M11-A5 (22). Drugs were dissolved as recommended by the manufacturer. Plates contained serial doubling dilutions of each antimicrobial agent. Either clavulanate was added to amoxicillin at a fixed ratio of 1:2 (310 strains tested in Leipzig) as recommended by the NCCLS (22) or MICs were determined in the presence of a fixed clavulanic acid concentration of 2 $\mu\text{g/ml}$ ($n = 331$, tested in Lille), as suggested by the French Committee on Antimicrobial Susceptibility Testing (1). In addition, French isolates were also tested at amoxicillin-clavulanic acid concentrations of 16 and 8, 8 and 4, 4 and 2, and 2 and 1 $\mu\text{g/ml}$, respectively. Reading of the MICs was performed after 48 h of incubation in an anaerobic chamber. If at that time bacterial growth was not sufficient as indicated by the control plates, incubation was continued for up to 5 days altogether. The MIC of an antibiotic for an organism was defined as the lowest concentration of an antimicrobial agent yielding no growth or a marked change in growth compared to that on the control plate.

All of the bacterial strains isolated in Lille were examined for β -lactamase production by the nitrocefin disk method.

The distribution of the MICs for the 641 bacterial strains is presented in Tables 1 to 10. At ≤ 2 $\mu\text{g/ml}$, garenoxacin inhibited 93% (597 of 641) of the isolates studied and was the most active of the quinolones tested against anaerobes. Among the *B. fragilis* group isolates, the rate of resistance to clindamycin was 30% in Lille and 13% in Leipzig. All strains of *B. fragilis* with decreased susceptibility to metronidazole were isolated at the Department of Microbiology in Lille. Almost all of the strains of the *B. fragilis* group (96.5%) were resistant to amoxicillin. All 130 *B. fragilis* strains examined in Lille produced β -lactamase. Addition of clavulanate enhanced the activity of amoxicillin against β -lactamase-producing strains. Resistance to imipenem due to carbapenemase production is still rare. It was found in one strain of *B. fragilis* from Lille and in one strain of *B. thetaiotaomicron* from Leipzig. β -Lactamase production was detected among 24 (66%) of 35 *Prevotella* species and 3 (15%) of 20 *Fusobacterium* species by the nitrocefin test (tested in Lille). β -Lactamase production can be assumed for 9 (45%)

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TABLE 8. Activity of imipenem against 641 anaerobes^a

Bacterium (no. of isolates)	% of strains inhibited by imipenem at concn (µg/ml) of:												
	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	>32	
<i>Bacteroides fragilis</i> (155)	1	24	56	47	18	5	3					1	
<i>Bacteroides thetaiotaomicron</i> (28)		2	4	12	8	1			1				
Other <i>Bacteroides</i> spp. (67)		2	10	23	23	7	2						
<i>B. fragilis</i> group (250)	1	28	70	82	49	13	5		1			1	
<i>Prevotella</i> spp. (55)	26	14	4	7	3	1							
<i>Fusobacterium</i> spp. (40)	19	13	3	2	2	1							
<i>Porphyromonas</i> spp. (20)	19	1											
<i>Bilophila wadsworthia</i> (19)	4	4	3	5	2	1							
Other gram-negative bacilli (2)	1	1											
<i>Veillonella</i> spp. (19)	8	7	1	1		2							
All gram-negative anaerobes (405)	78	68	81	97	56	18	5		1			1	
<i>Clostridium</i> spp. (54)	8	16	13	5	2	5	3	2					
<i>Clostridium difficile</i> (46)								3	34	9			
<i>Bifidobacterium</i> spp. (12)	2	4	2	2	1	1							
<i>Eggerthella lenta</i> (12)	5	2			5								
<i>Eubacterium aerofaciens</i> (4)	4												
<i>Actinomyces</i> spp. (1)	1												
<i>Propionibacterium</i> spp. (21)	18	3											
Gram-positive cocci (86)	71	11	2		1	1							
All gram-positive anaerobes (236)	109	36	17	7	9	7	6	36	9				

^a For details, see the footnotes to Table 1.

fragilis group strains examined in Lille, France. More resistant isolates were seen among the non-*B. fragilis* species than among the *B. fragilis* strains. Snyderman et al. (27) and Aldridge et al. (5) reported similar results and found that the resistance to clindamycin had increased among members of the *B. fragilis* group in recent years to 29% (5) and 16% (27). Betriu et al. (9) and Lubbe et al. (19) identified clindamycin resistance rates of 34 and 29%, respectively.

In summary, garenoxacin had the broadest antianaerobic activity among the quinolones tested, inhibiting almost all of

TABLE 9. Activity of clindamycin against 641 anaerobes^a

Bacterium (no. of isolates)	% of strains inhibited by clindamycin at concn (µg/ml) of:												
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64	
<i>Bacteroides fragilis</i> (155)	6	6	21	50	31	18	6	1				16	
<i>Bacteroides thetaiotaomicron</i> (28)	2			1	1	6	6	2	2			8	
Other <i>Bacteroides</i> spp. (67)	6		1	5	9	12	8	1	1			24	
<i>B. fragilis</i> group (250)	14	6	22	56	41	36	20	4	3			48	
<i>Prevotella</i> spp. (55)	40	2	4	5	1						1	2	
<i>Fusobacterium</i> spp. (40)	21	14	2	1	1	1							
<i>Porphyromonas</i> spp. (20)	20												
<i>Bilophila wadsworthia</i> (19)	2	6	11										
Other gram-negative bacilli (2)	2												
<i>Veillonella</i> spp. (19)	4	5	10										
All gram-negative anaerobes (405)	103	33	49	62	42	38	20	4	3		1	50	
<i>Clostridium</i> spp. (54)	17	2	2	4	2	4	10	2	3	1		7	
<i>Clostridium difficile</i> (46)								2	6	18	2	18	
<i>Bifidobacterium</i> spp. (12)	9			2								1	
<i>Eggerthella lenta</i> (12)	7	1	2	2									
<i>Eubacterium aerofaciens</i> (4)	3	1											
<i>Actinomyces</i> spp. (1)	1												
<i>Propionibacterium</i> spp. (21)	1	10	2	3	3				1	1			
Gram-positive cocci (86)	31	14	10	10	8	3	3	2	1	2	1	1	
All gram-positive anaerobes (236)	69	28	16	18	13	10	15	10	22	6	2	27	

^a For details, see the footnotes to Table 1.TABLE 10. Activity of metronidazole against 641 anaerobes^a

Bacterium (no. of isolates)	% of strains inhibited by metronidazole at concn (µg/ml) of:												
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64	
<i>Bacteroides fragilis</i> (155)		2	12	60	67	6	4	2	1			1	
<i>Bacteroides thetaiotaomicron</i> (28)		2		13	12	1							
Other <i>Bacteroides</i> spp. (67)				1	26	36	3	1					
<i>B. fragilis</i> group (250)		4	13	99	115	10	4	3	1			1	
<i>Prevotella</i> spp. (55)	3	6	13	16	12	3	2						
<i>Fusobacterium</i> spp. (40)	17	10	7	5	1								
<i>Porphyromonas</i> spp. (20)	11	5	3	1									
<i>Bilophila wadsworthia</i> (19)	16	3											
Other gram-negative bacilli (2)	1							1					
<i>Veillonella</i> spp. (19)	2			1	6	8	2						
All gram-negative anaerobes (405)	50	28	36	122	133	23	8	3	1			1	
<i>Clostridium</i> spp. (54)	6	7	9	22	8	1	1						
<i>Clostridium difficile</i> (46)				2	11	29	2	1	1				
<i>Bifidobacterium</i> spp. (12)											3	2	
<i>Eggerthella lenta</i> (12)	1		3	6	1							1	
<i>Eubacterium aerofaciens</i> (4)				3	1								
<i>Actinomyces</i> spp. (1)	1												
<i>Propionibacterium</i> spp. (21)												21	
Gram-positive cocci (86)	24	10	30	14	3	1						4	
All gram-positive anaerobes (236)	32	17	44	56	41	6	1	1	1	3	2	32	

^a For details, see the footnotes to Table 1.

the anaerobic bacterial strains tested. Clinical trials to establish the potency of garenoxacin as a therapeutic option are necessary.

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