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Increased Activity of a New Chlorofluoroquinolone, BAY y 3118, Compared with Activities of Ciprofloxacin, Sparfloxacin, and Other Antimicrobial Agents against Anaerobic Bacteria

KENNETH E. ALDRIDGE

Section of Infectious Diseases, Department of Medicine, Louisiana State University Medical Center, New Orleans, Louisiana 70112

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A total of 435 clinical isolates of anaerobes were tested with a broth microdilution method to determine the activity of BAY y 3118 compared with those of other agents against anaerobic bacteria. All strains of *Bacteroides capillosus*, *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp., *Clostridium* spp., *Eubacterium* spp., *Peptostreptococcus* spp., and *Veillonella parvula* were susceptible (MICs of ≤2 μg/ml) to BAY y 3118. Against the 315 strains of the *Bacteroides fragilis* group, five strains required elevated MICs (≥4 μg/ml) of BAY y 3118. Only imipenem and metronidazole were active against all anaerobes. Overall, BAY y 3118 was more active than ciprofloxacin, sparfloxacin, piperacillin, cefotaxime, and clindamycin against the test isolates.

Newer fluoroquinolone antimicrobial agents such as ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, and pefloxacin have been shown to have good activity against aerobic bacteria but usually have poor activity against most anaerobes, particularly the *Bacteroides fragilis* group (1, 3, 6, 7, 11). Some newer quinolones, such as sparfloxacin and WIN 57273, have increased activity against anaerobes, including the various species of the *B. fragilis* group (4, 12). BAY y 3118 is a new chlorofluoroquinolone. This study was performed to determine the in vitro activity of BAY y 3118 compared with those of other antimicrobial agents against a variety of clinically significant anaerobes.

A total of 435 nonduplicate, clinical isolates were randomly selected and tested at Louisiana State University Medical Center in New Orleans. Each isolate was identified by using selective media, biochemical profiles, and gas-liquid chromatography (5, 10). Test antimicrobial agents were supplied by the following manufacturers: BAY y 3118 and ciprofloxacin, Miles Pharmaceuticals, West Haven, Conn.; sparfloxacin, Parke-Davis, Warner Lambert Co., Ann Arbor, Mich.; piperacillin, Lederle Laboratories, Pearl River, N.Y.; imipenem, Merck Sharp & Dohme, Rahway, N.J.; cefotaxime, Hoechst-Roussel Pharmaceuticals, Somerville, N.J.; clindamycin, The Upjohn Co., Kalamazoo, Mich.; and metronidazole, G. D. Searle, Skokie, Ill. Susceptibility studies were performed with each isolate by using a broth microdilution method as described by the National Committee for Clinical Laboratory Standards (8). Serial twofold dilutions of each antimicrobial agent were prepared in Anaerobe broth MIC (Difco, Detroit, Mich.) within a dilution range of 0.02 to 256 μg/ml. When more fastidious anaerobes, including *Porphyromonas*, *Fusobacterium*, *Veillonella*, and some *Prevotella* species, were tested, the test medium was supplemented with 3% lysed horse blood. The inoculum was prepared by suspending growth from 24-h blood agar plates to a no. 1 McFarland standard and dilution to a final inoculum of 10^5 CFU per well (10^6 CFU/ml). All plates were incubated in an anaerobic chamber (10% CO_2, 10% H_2, 80% N_2) for 48 h at 37°C and read. The MIC was defined as the lowest concentration of each agent that inhibited the visible growth of the test isolates. *B. fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *Eubacterium lentum* ATCC 43055, and *Clostridium perfringens* ATCC 13124 were used as reference quality control strains.

Table 1 compares the in vitro activity of BAY y 3118 with those of other compounds against the various anaerobes. Against the *B. fragilis* group, BAY y 3118 inhibited >98% of the strains at 2 μg/ml. The strains requiring MICs of ≥4 μg/ml were two strains of *B. thetaiotaomicron*, two strains of *Bacteroides uniformis*, and one strain of *Bacteroides vulgatus*. Sparfloxacin inhibited 94% of the *B. fragilis* group, while ciprofloxacin inhibited 6% at 2 μg/ml. Only metronidazole and imipenem inhibited all of the *B. fragilis* group strains at the respective breakpoints. For the *B. fragilis* group overall, cefotaxime, piperacillin, and clindamycin inhibited 81, 88, and 85% of the strains, respectively. Against *Bacteroides capillosus* strains, BAY y 3118, imipenem, and clindamycin were the most active agents, each with a MIC for 90% of strains tested (MIC_{90}) of 0.06 μg/ml, and no strain with resistance to any of the test agents was detected. BAY y 3118 was appreciably more active than ciprofloxacin and sparfloxacin against strains of *Prevotella bivia*, *Prevotella disiens*, and *Peptostreptococcus asaccharolytica* and had activity comparable to those of imipenem and clindamycin.

BAY y 3118 was as active as imipenem, clindamycin, and metronidazole against *Fusobacterium* spp. but was 4 to 6 twofold dilutions more active than ciprofloxacin, cefotaxime, sparfloxacin, and piperacillin. All strains of *Clostridium* spp. and *Eubacterium* spp. were susceptible to BAY y 3118, which had lower MIC_{90}s than all of the other agents. All strains of *Peptostreptococcus* spp. and *Veillonella parvula* were susceptible to BAY y 3118 and the other agents, with the exception of a strain from each group being resistant to ciprofloxacin.

BAY y 3118 MICs for the quality control strains (15 values for each) were as follows: *B. fragilis* ATCC 25285, 0.03 μg/ml; *B. thetaiotaomicron* ATCC 29741, 0.12 to 0.5 μg/ml; *E. lentum* ATCC 43055, 0.03 to 0.12 μg/ml; and *C. perfringens* ATCC 13124, 0.03 to 0.06 μg/ml.

Our results confirm and extend the data regarding the in vitro activity of BAY y 3118 against anaerobes, particularly against those in the *B. fragilis* group. In the present study, we identified 5 of 435 (1%) anaerobes which were resistant (MICs of ≥4 μg/ml) to BAY y 3118; all were strains of the *B. fragilis* group. All other anaerobes were susceptible. In a similar study,

TABLE 1. Comparison of the in vitro activities of BAY y 3118 and other agents against clinically important anaerobes

Organism (no. of strains tested) and agent	Concn (μg/ml)				% Susceptible[a]
	Range	MIC	MIC_{50}	MIC_{90}	
Bacteroides distasonis (24)					
BAY y 3118	0.016–0.5	0.063	0.063	0.12	100, 100, 100
Ciprofloxacin	2–16	8	8	16	0, 4, 42
Sparfloxacin	0.5–16	2	2	2	42, 96, 96
Piperacillin	1–128	4	4	128	67, 83, 100
Imipenem	0.03–2	0.5	0.25	0.5	100, 100, 100
Cefotaxime	0.5–64	64	4	64	67, 75, 100
Clindamycin	0.03–8	8	2	8	54, 63, 100
Metronidazole	0.5–1	1	1	1	100, 100, 100
Bacteroides fragilis (165)					
BAY y 3118	0.02–1	0.06	0.06	0.12	100, 100, 100
Ciprofloxacin	2–16	4	4	16	0, 7, 75
Sparfloxacin	0.25–16	1	1	2	78, 93, 95
Piperacillin	0.12–128	2	4	64	84, 91, 100
Imipenem	0.02–2	0.03	0.06	0.25	100, 100, 100
Cefotaxime	0.25–64	8	8	64	79, 82, 100
Clindamycin	0.02–8	0.5	0.5	2	87, 90, 91
Metronidazole	0.12–2	1	1	1	100, 100, 100
Bacteroides ovatus (34)					
BAY y 3118	0.03–1	0.25	0.25	0.5	100, 100, 100
Ciprofloxacin	2–16	16	16	16	0, 3, 9
Sparfloxacin	0.5–8	2	2	2	18, 91, 97
Piperacillin	0.5–128	8	16	128	79, 88, 100
Imipenem	0.03–0.5	0.12	0.12	0.25	100, 100, 100
Cefotaxime	0.12–128	32	32	128	41, 77, 94
Clindamycin	0.25–16	8	4	16	44, 65, 92
Metronidazole	0.25–2	1	1	1	100, 100, 100
Bacteroides thetaiotaomicron (51)					
BAY y 3118	0.03–>8	0.25	0.25	0.5	94, 96, 98
Ciprofloxacin	2–16	16	16	16	0, 6, 14
Sparfloxacin	0.5–16	1	2	4	49, 88, 92
Piperacillin	1–256	16	16	64	88, 90, 99
Imipenem	0.03–1	0.12	0.12	0.25	100, 100, 100
Cefotaxime	0.5–128	32	32	64	24, 82, 97
Clindamycin	0.12–8	2	2	4	34, 65, 92
Metronidazole	0.12–1	1	1	1	100, 100, 100
Bacteroides uniformis (13)					
BAY y 3118	0.12–8	0.25	0.25	4	85, 85, 100
Ciprofloxacin	16–≥32	16	16	≥32	0, 0, 0
Sparfloxacin	1–16	2	2	8	23, 85, 85
Piperacillin	4–256	8	16	128	77, 77, 93
Imipenem	0.12–0.25	0.12	0.12	0.25	100, 100, 100
Cefotaxime	4–128	64	16	128	54, 69, 88
Clindamycin	0.02–8	1	1	8	54, 69, 85
Metronidazole	0.06–1	1	0.5	1	100, 100, 100
Bacteroides vulgatus (28)					
BAY y 3118	0.03–8	0.06	0.06	1	93, 96, 96
Ciprofloxacin	2–16	16	16	16	0, 4, 11
Sparfloxacin	0.5–16	0.5	1	16	86, 89, 89
Piperacillin	1–256	4	4	128	68, 75, 95
Imipenem	0.03–2	0.5	0.25	1	100, 100, 100
Cefotaxime	0.25–128	1	4	128	82, 86, 98
Clindamycin	0.03–8	0.03	0.12	8	86, 86, 86
Metronidazole	0.12–1	0.5	0.5	1	100, 100, 100
Bacteroides capillosus (10)					
BAY y 3118	0.03–0.06	0.06	0.06	0.06	100, 100, 100
Ciprofloxacin	0.06–2	2	2	2	30, 100, 100
Sparfloxacin	0.12–2	1	1	2	60, 100, 100
Piperacillin	0.06–16	2	4	16	100, 100, 100

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TABLE 1—*Continued*

Organism (no. of strains tested) and agent	Concn (μg/ml)				% Susceptible[a]
	Range	MIC	MIC_{50}	MIC_{90}	
Imipenem	0.03–0.12	0.03	0.03	0.06	100, 100, 100
Cefotaxime	0.03–8	0.25	0.5	4	100, 100, 100
Clindamycin	0.03–0.06	0.03	0.03	0.06	100, 100, 100
Metronidazole	0.25–4	0.5	0.5	1	100, 100, 100
Prevotella bivia (23)					
BAY y 3118	0.03–1	0.25	0.25	0.5	100, 100, 100
Ciprofloxacin	0.5–16	16	16	16	17, 17, 17
Sparfloxacin	1–16	16	16	16	4, 17, 35
Piperacillin	0.25–64	8	8	32	96, 100, 100
Imipenem	0.03–0.06	0.03	0.03	0.06	100, 100, 100
Cefotaxime	0.03–32	4	4	16	91, 100, 100
Clindamycin	0.03–0.06	0.03	0.03	0.03	100, 100, 100
Metronidazole	0.25–4	2	2	2	100, 100, 100
Prevotella disiens (10)					
BAY y 3118	0.03	0.03	0.03	0.03	100, 100, 100
Ciprofloxacin	1–2	1	1	2	100, 100, 100
Sparfloxacin	2–4	2	2	2	0, 90, 100
Piperacillin	1–64	2	4	16	90, 100, 100
Imipenem	0.03–0.06	0.03	0.03	0.06	100, 100, 100
Cefotaxime	0.5–16	0.5	0.5	8	100, 100, 100
Clindamycin	0.03	0.03	0.03	0.03	100, 100, 100
Metronidazole	0.5–2	1	1	1	100, 100, 100
Porphyromonas asaccharolytica (10)					
BAY y 3118	0.03–0.12	0.03	0.03	0.06	100, 100, 100
Ciprofloxacin	0.25–16	0.5	0.5	1	90, 90, 90
Sparfloxacin	0.5–4	0.5	1	2	60, 90, 100
Piperacillin	0.06–32	0.06	0.25	8	100, 100, 100
Imipenem	0.03–0.25	0.03	0.32	0.12	100, 100, 100
Cefotaxime	0.03–8	0.03	0.25	2	100, 100, 100
Clindamycin	0.03–0.06	0.03	0.03	0.06	100, 100, 100
Metronidazole	0.03–2	0.5	0.5	2	100, 100, 100
Fusobacterium spp. (13)[b]					
BAY y 3118	0.03–0.5	0.03	0.03	0.06	100, 100, 100
Ciprofloxacin	0.5–4	1	1	1	92, 92, 100
Sparfloxacin	0.12–4	0.25	0.25	2	85, 92, 100
Piperacillin	0.06–16	0.06	0.06	4	100, 100, 100
Imipenem	0.03–1	0.03	0.03	0.06	100, 100, 100
Cefotaxime	0.03–4	0.03	0.06	1	100, 100, 100
Clindamycin	0.03–2	0.03	0.03	0.06	100, 100, 100
Metronidazole	0.03–1	0.06	0.06	0.25	100, 100, 100
Clostridium spp. (12)[c]					
BAY y 3118	0.06–0.25	0.06	0.06	0.25	100, 100, 100
Ciprofloxacin	0.25–8	0.25	0.5	4	67, 83, 92
Sparfloxacin	0.12–2	0.12	0.25	2	83, 100, 100
Piperacillin	0.06–32	0.06	0.25	16	100, 100, 100
Imipenem	0.03–4	0.12	0.12	2	100, 100, 100
Cefotaxime	0.03–32	0.03	1	8	92, 100, 100
Clindamycin	0.03–8	0.03	0.12	2	92, 92, 100
Metronidazole	0.03–2	0.5	0.5	2	100, 100, 100
Eubacterium spp. (18)[d]					
BAY y 3118	0.03–0.06	0.03	0.03	0.03	100, 100, 100
Ciprofloxacin	0.3–2	0.5	0.5	2	83, 100, 100
Sparfloxacin	0.03–0.5	0.5	0.25	0.5	100, 100, 100
Piperacillin	0.5–16	16	8	16	100, 100, 100
Imipenem	0.3–1	0.25	0.25	0.5	100, 100, 100
Cefotaxime	0.12–128	128	128	128	33, 42, 42
Clindamycin	0.3–1	0.12	0.12	1	100, 100, 100
Metronidazole	0.25–0.5	0.25	0.25	0.25	100, 100, 100
Peptostreptococcus spp. (14)[e]					
BAY y 3118	0.03–2	0.06	0.06	2	86, 100, 100

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TABLE 1—*Continued*

Organism (no. of strains tested) and agent	Concn (μg/ml)				% Susceptible[a]
	Range	MIC	MIC_{50}	MIC_{90}	
Ciprofloxacin	0.5–4	2	2	2	29, 93, 100
Sparfloxacin	0.12–1	0.25	0.25	0.5	100, 100, 100
Piperacillin	0.06–16	0.06	0.06	16	100, 100, 100
Imipenem	0.03–1	0.03	0.03	1	100, 100, 100
Cefotaxime	0.03–16	0.06	0.06	8	100, 100, 100
Clindamycin	0.06–2	0.06	0.12	0.5	100, 100, 100
Metronidazole	0.12–2	0.5	0.5	1	100, 100, 100
Veillonella parvula (10)					
BAY y 3118	0.03–0.12	0.03	0.03	0.06	100, 100, 100
Ciprofloxacin	0.03–4	0.03	0.06	0.5	90, 90, 100
Sparfloxacin	0.03–2	0.03	0.03	0.25	90, 100, 100
Piperacillin	0.03–32	0.06	0.12	16	100, 100, 100
Imipenem	0.03–0.12	0.06	0.03	0.06	100, 100, 100
Cefotaxime	0.03–4	0.03	0.12	1	100, 100, 100
Clindamycin	0.03–1	0.03	0.03	0.12	100, 100, 100
Metronidazole	0.12–2	0.5	0.5	2	100, 100, 100

[a] Susceptibility results are expressed at the breakpoint (underlined) and 1 dilution above and below the breakpoint. The following susceptibility breakpoints (in micrograms per milliliter), as recommended by the National Committee for Clinical Laboratory Standards (8) or the manufacturer, were used to determine susceptibility: 2, BAY y 3118, ciprofloxacin, and sparfloxacin; 4, clindamycin; 8, imipenem; 16, metronidazole; 32, cefotaxime; and 64, piperacillin. Cutoff values for BAY y 3118 and sparfloxacin were arbitrarily chosen because no cutoff values have been approved by the Food and Drug Administration.

[b] Includes nine *F. nucleatum* and four *F. necrophorum* strains.

[c] Includes four *C. perfringens*, one *C. cadaveris*, one *C. innocuum*, two *C. ramosum*, and two *C. butyricum* strains, one *C. septicum* strain, and one *C. subterminale* strain.

[d] Includes 13 *E. lentum* and 4 *E. limosum* strains and 1 *E. aerofaciens* strain.

[e] Includes 3 *P. anaerobius* and 10 *P. asaccharolyticus* strains and 1 *P. tetradius* strain.

Wexler et al. (13) reported that BAY y 3118 possesses good activity against a variety of anaerobes. In that study, all strains of the *B. fragilis* group were susceptible to BAY y 3118, although one strain of *Bacteroides ovatus* required a MIC of 2 μg/ml. In addition, one strain of *Fusobacterium nucleatum* required a MIC of 4 μg/ml. Fass (2) reported that all test strains of *B. fragilis* and *B. thetaiotaomicron* were susceptible to BAY y 3118, with MIC_{90}s of 0.12 and 0.5 μg/ml, respectively; however, one or more strains of *B. thetaiotaomicron* required an elevated MIC of 1 μg/ml. Pankuch et al. (9) reported no resistance to BAY y 3118 among 428 anaerobes, although elevated MICs (1 to 2 μg/ml) were noted among fusobacteria.

All of the data presented above indicate the expanded in vitro spectrum of BAY y 3118 to include anaerobes compared with the spectra of the other available quinolone compounds. Pharmacokinetic and clinical studies are needed to define the role of BAY y 3118 in anaerobic infections. Unfortunately, severe phototoxicity associated with use of BAY y 3118 has been identified in humans and may limit clinical development of the drug.

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