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Activity of WY-49605 Compared with Those of Amoxicillin, Amoxicillin-Clavulanate, Imipenem, Ciprofloxacin, Cefaclor, Cefpodoxime, Cefuroxime, Clindamycin, and Metronidazole against 384 Anaerobic Bacteria

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The National Committee for Clinical Laboratory Standards agar dilution method was used to compare the in vitro activity of WY-49605 (also called SUN/SY 5555 and ALP-201), a new broad-spectrum oral penem, to those of amoxicillin, amoxicillin-clavulanate, imipenem, ciprofloxacin, cefaclor, cefpodoxime, cefuroxime, clindamycin, and metronidazole against 384 clinically isolated anaerobes. These anaerobic organisms included 90 strains from the *Bacteroides fragilis* group, 87 *Prevotella* and *Porphyromonas* strains, non-*B. fragilis* group *Bacteroides* strains, 56 fusobacteria, 55 peptostreptococci, 49 gram-positive non-spore-forming rods, and 47 clostridia. Overall, WY-49605 had an MIC range of 0.015 to 8.0 μg/ml, an MIC at which 50% of the isolates are inhibited (MIC_{50}) of 0.25 μg/ml, and an MIC at which 90% of the isolates are inhibited (MIC_{90}) of 2.0 μg/ml. Good activity against all anaerobe groups was observed, except for *Clostridium difficile* and lactobacilli (MIC_{50}s of 4.0 and 2.0 μg/ml, respectively, and MIC_{90}s of 8.0 and 2.0 μg/ml, respectively). Imipenem had an MIC_{50} of 0.03 μg/ml and an MIC_{90} of 0.25 μg/ml. Ciprofloxacin was much less active (MIC_{50} of 2.0 μg/ml and MIC_{90} of 16.0 μg/ml). By comparison, all oral β-lactams were less active than WY-49605, with susceptibilities as follows: amoxicillin MIC_{50} of 8.0 μg/ml and MIC_{90} of >256.0 μg/ml), amoxicillin-clavulanate MIC_{50} of 1.0 μg/ml and MIC_{90} of 8.0 μg/ml, cefaclor MIC_{50} of 8.0 μg/ml and MIC_{90} of >32.0 μg/ml, cefpodoxime MIC_{50} of 4.0 μg/ml and MIC_{90} of >32.0 μg/ml, and cefuroxime MIC_{50} of 4.0 μg/ml and MIC_{90} of >32.0 μg/ml. Clindamycin was active against all groups except some members of the *B. fragilis* group, *Fusobacterium varium*, and some clostridia (overall MIC_{50} of 0.5 μg/ml and overall MIC_{90} of 8.0 μg/ml). Metronidazole was active (MIC of ≤4.0 μg/ml) against all gram-negative anaerobic rods, but most gram-positive non-spore-forming rods, some peptostreptococci, and some clostridia were less susceptible. To date, WY-49605 is the most active oral β-lactam against anaerobes: these results suggest clinical evaluation for clinical indications suitable for oral therapy.

Anaerobes are established causes of serious human infections, especially in debilitated hosts (2, 23). Although infections caused by members of the *Bacteroides fragilis* group occur most commonly, infections caused by other gram-negative anaerobic rods, as well as by gram-positive cocci and rods, are increasingly encountered (2, 23). The susceptibility spectra of clinically isolated anaerobes are changing. Although β-lactamase production and concomitant resistance to β-lactams are the rule in the *B. fragilis* group, both phenomena are increasingly encountered in non-*B. fragilis* group *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium* species (3–8, 10, 16, 19). β-Lactamase production has also been described in *Clostridium butyricum*, *Clostridium ramosum*, and *Clostridium clostridioforme* (9). Metronidazole resistance is the rule among gram-positive non-spore-forming rods but has also been reported in peptostreptococci, non-*Clostridium perfringens* clostridia, and members of the *B. fragilis* group (8, 12). Additionally, clindamycin resistance is not unusual among anaerobic gram-negative rods (8, 10).

With the exception of amoxicillin-clavulanate, oral β-lactam antimicrobial agents are not very active against β-lactamase-producing anaerobes, and there is a need for more oral agents which are active against these organisms. WY-49605 (also called SUN/SY 5555 and ALP-201), is a novel oral penem with a broad spectrum of activity against gram-negative and -positive aerobic and anaerobic strains. Its chemical structure has been described by Nishino and coworkers as sodium (5*R*, 6*S*, 8*R*, 2′*R*)-2-(2′-tetrahydrofuryl)-6-hydroxyethylpenem-3-carboxylate (18). This compound is stable to most classes of β-lactamases and seems less epileptogenic than impinenem (11, 14, 15, 18, 20–22, 24). This study compared the in vitro activity of WY-49605 to those of amoxicillin, amoxicillin-clavulanate, imipenem, ciprofloxacin, cefaclor, cefpodoxime, cefuroxime, clindamycin, and metronidazole against 384 clinically isolated anaerobes.

MATERIALS AND METHODS

Bacteria. All anaerobic strains were clinical isolates which were identified by standard procedures (2, 13, 23) and kept frozen in double-strength skim milk at −70°C until use. Strains were collected from the Hershey Medical Center, Case Western Reserve University, and several other institutions around the United States (6–8) between 1990 and 1993. Prior to testing, strains were subcultured twice onto enriched sheep

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TABLE 1. Antimicrobial susceptibilities of anaerobic strains

Organism (no. of strains tested/no. of β-lactamase-positive strains) and antimicrobial agent	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Bacteroides fragilis (30/30)			
WY-49605	0.06–4.0	0.5	2.0
Amoxicillin	0.5–>256.0	64.0	>256.0
Amoxicillin-clavulanate	0.25–4.0	1.0	4.0
Imipenem	0.015–0.25	0.06	0.125
Ciprofloxacin	1.0–32.0	8.0	16.0
Cefaclor	0.5–>32.0	32.0	>32.0
Cefpodoxime	0.5–>32.0	32.0	>32.0
Cefuroxime	0.5–>32.0	32.0	>32.0
Clindamycin	0.125–>16.0	0.25	2.0
Metronidazole	0.25–4.0	2.0	4.0
Bacteroides thetaiotaomicron (15/15)			
WY-49605	0.03–2.0	0.125	2.0
Amoxicillin	0.25–>256.0	64.0	128.0
Amoxicillin-clavulanate	0.125–4.0	1.0	2.0
Imipenem	0.015–0.125	0.03	0.06
Ciprofloxacin	0.25–8.0	4.0	8.0
Cefaclor	0.25–>32.0	32.0	>32.0
Cefpodoxime	0.125–>32.0	32.0	>32.0
Cefuroxime	0.125–>32.0	32.0	>32.0
Clindamycin	0.125–2.0	0.5	2.0
Metronidazole	0.125–4.0	2.0	4.0
Bacteroides ovatus (15/15)			
WY-49605	0.03–4.0	0.5	4.0
Amoxicillin	1.0–>256.0	256.0	>256.0
Amoxicillin-clavulanate	0.25–16.0	2.0	8.0
Imipenem	0.015–1.0	0.03	0.125
Ciprofloxacin	4.0–>64.0	32.0	>64.0
Cefaclor	16.0–>32.0	>32.0	>32.0
Cefpodoxime	8.0–>32.0	>32.0	>32.0
Cefuroxime	4.0–>32.0	>32.0	>32.0
Clindamycin	0.25–>16.0	1.0	>16.0
Metronidazole	0.25–2.0	1.0	2.0
Bacteroides distasonis (15/15)			
WY-49605	0.03–2.0	0.5	1.0
Amoxicillin	0.5–>256.0	64.0	>256.0
Amoxicillin-clavulanate	0.125–32.0	2.0	32.0
Imipenem	0.015–0.25	0.06	0.25
Ciprofloxacin	1.0–>64.0	4.0	16.0
Cefaclor	0.25–>32.0	16.0	>32.0
Cefpodoxime	0.125–>32.0	8.0	>32.0
Cefuroxime	0.125–>32.0	8.0	>32.0
Clindamycin	0.125–2.0	0.25	2.0
Metronidazole	0.25–2.0	1.0	2.0
Bacteroides vulgatus (15/15)			
WY-49605	0.06–2.0	0.5	2.0
Amoxicillin	0.5–>256.0	>256.0	>256.0
Amoxicillin-clavulanate	0.25–8.0	2.0	8.0
Imipenem	0.015–0.125	0.125	0.125
Ciprofloxacin	1.0–64.0	8.0	32.0
Cefaclor	2.0–>32.0	>32.0	>32.0
Cefpodoxime	1.0–>32.0	>32.0	>32.0
Cefuroxime	1.0–>32.0	>32.0	>32.0
Clindamycin	0.25–>16.0	0.5	>16.0
Metronidazole	0.25–4.0	2.0	4.0
Bacteroides fragilis group (90/90)			
WY-49605	0.03–4.0	0.5	2.0
Amoxicillin	0.25–>256.0	64.0	>256.0
Amoxicillin-clavulanate	0.125–32.0	1.0	8.0
Imipenem	0.015–1.0	0.06	0.125
Ciprofloxacin	0.25–>64.0	8.0	32.0
Cefaclor	0.25–>32.0	32.0	>32.0
Cefpodoxime	0.125–>32.0	32.0	>32.0
Cefuroxime	0.125–>32.0	32.0	>32.0
Clindamycin	0.125–>16.0	0.25	4.0
Metronidazole	0.125–4.0	2.0	4.0
Prevotella bivia (23/19)			
WY-49605	0.015–2.0	0.06	2.0
Amoxicillin	0.5–32.0	16.0	32.0
Amoxicillin-clavulanate	0.125–32.0	1.0	16.0
Imipenem	0.015–2.0	0.015	0.5
Ciprofloxacin	1.0–16.0	8.0	16.0
Cefaclor	0.06–>32.0	2.0	>32.0
Cefpodoxime	0.06–>32.0	1.0	>32.0
Cefuroxime	0.06–>32.0	2.0	>32.0
Clindamycin	0.125–4.0	0.25	0.25
Metronidazole	1.0–4.0	2.0	4.0
Prevotella disiens (13/10)			
WY-49605	0.06–0.25	0.125	0.25
Amoxicillin	0.125–>256.0	8.0	>256.0
Amoxicillin-clavulanate	0.125–8.0	0.5	4.0
Imipenem	0.015–0.25	0.03	0.125
Ciprofloxacin	0.25–16.0	2.0	16.0
Cefaclor	0.125–>32.0	4.0	>32.0
Cefpodoxime	0.06–>32.0	4.0	32.0
Cefuroxime	0.06–>32.0	4.0	32.0
Clindamycin	0.125–1.0	0.25	0.25
Metronidazole	0.5–4.0	2.0	4.0
Prevotella melaninogenica (10/8)			
WY-49605	0.06–1.0	0.25	1.0
Amoxicillin	0.125–>256.0	16.0	>256.0
Amoxicillin-clavulanate	0.125–8.0	4.0	8.0
Imipenem	0.015–0.5	0.125	0.5
Ciprofloxacin	0.25–16.0	4.0	16.0
Cefaclor	0.06–32.0	16.0	32.0
Cefpodoxime	0.06–>32.0	8.0	>32.0
Cefuroxime	0.06–>32.0	8.0	>32.0
Clindamycin	0.125–2.0	0.5	2.0
Metronidazole	1.0–4.0	2.0	4.0
Prevotella intermedia (12/12)			
WY-49605	0.125–2.0	0.5	2.0
Amoxicillin	0.25–>256.0	64.0	>256.0
Amoxicillin-clavulanate	0.125–8.0	4.0	8.0
Imipenem	0.015–0.125	0.125	0.125
Ciprofloxacin	1.0–16.0	4.0	16.0
Cefaclor	2.0–>32.0	16.0	>32.0
Cefpodoxime	1.0–>32.0	8.0	>32.0
Cefuroxime	1.0–>32.0	8.0	>32.0
Clindamycin	0.125–2.0	0.25	2.0
Metronidazole	1.0–4.0	1.0	4.0
Miscellaneous strains[a] (29/28)			
WY-49605	0.03–4.0	0.125	1.0
Amoxicillin	0.25–>256.0	8.0	>256.0
Amoxicillin-clavulanate	0.125–8.0	1.0	8.0
Imipenem	0.015–0.5	0.06	0.5
Ciprofloxacin	0.25–16.0	2.0	16.0
Cefaclor	0.125–>32.0	16.0	>32.0

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TABLE 1—*Continued*

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TABLE 1—*Continued*

Organism (no. of strains tested/no. of β-lactamase-positive strains) and antimicrobial agent	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Cefpodoxime	0.06–>32.0	16.0	>32.0
Cefuroxime	0.06–>32.0	8.0	>32.0
Clindamycin	0.25–1.0	0.5	1.0
Metronidazole	1.0–4.0	1.0	4.0
Non-*B. fragilis Bacteroides*, *Prevotella*, and *Porphyromonas* spp. (87/77)			
WY-49605	0.015–4.0	0.125	1.0
Amoxicillin	0.125–>256.0	16.0	>256.0
Amoxicillin-clavulanate	0.125–32.0	1.0	8.0
Imipenem	0.015–2.0	0.06	0.5
Ciprofloxacin	0.25–16.0	4.0	16.0
Cefaclor	0.06–>32.0	8.0	>32.0
Cefpodoxime	0.06–>32.0	8.0	>32.0
Cefuroxime	0.06–>32.0	8.0	>32.0
Clindamycin	0.125–4.0	0.25	1.0
Metronidazole	0.5–4.0	2.0	4.0
Fusobacterium nucleatum (13/3)			
WY-49605	0.015–0.25	0.06	0.25
Amoxicillin	0.125–256.0	0.5	128.0
Amoxicillin-clavulanate	0.125–4.0	0.25	4.0
Imipenem	0.015–0.25	0.015	0.125
Ciprofloxacin	0.25–8.0	2.0	4.0
Cefaclor	0.06–>32.0	0.125	>32.0
Cefpodoxime	0.06–>32.0	0.25	16.0
Cefuroxime	0.06–>32.0	0.25	16.0
Clindamycin	0.25–>16.0	0.25	4.0
Metronidazole	0.125–4.0	1.0	2.0
Fusobacterium necrophorum (10/1)			
WY-49605	0.015–0.125	0.06	0.125
Amoxicillin	0.125–8.0	0.25	8.0
Amoxicillin-clavulanate	0.125–0.5	0.25	0.5
Imipenem	0.015–0.06	0.015	0.06
Ciprofloxacin	0.5–4.0	2.0	4.0
Cefaclor	0.06–16.0	0.25	16.0
Cefpodoxime	0.06–16.0	0.25	16.0
Cefuroxime	0.06–4.0	0.25	4.0
Clindamycin	0.125–1.0	0.25	1.0
Metronidazole	0.125–4.0	0.25	2.0
Fusobacterium mortiferum (15/11)			
WY-49605	0.03–4.0	0.5	1.0
Amoxicillin	0.125–>256.0	8.0	256.0
Amoxicillin-clavulanate	0.125–8.0	2.0	8.0
Imipenem	0.015–0.25	0.06	0.25
Ciprofloxacin	0.5–16.0	2.0	4.0
Cefaclor	1.0–>32.0	1.0	32.0
Cefpodoxime	0.25–>32.0	1.0	32.0
Cefuroxime	0.25–>32.0	1.0	32.0
Clindamycin	0.25–2.0	0.5	2.0
Metronidazole	0.5–4.0	1.0	4.0
Fusobacterium varium (18/16)			
WY-49605	0.06–4.0	0.5	2.0
Amoxicillin	0.125–>256.0	32.0	>256.0
Amoxicillin-clavulanate	0.125–32.0	4.0	8.0
Imipenem	0.015–0.5	0.125	0.5
Ciprofloxacin	0.5–16.0	4.0	16.0
Cefaclor	0.06–>32.0	8.0	>32.0
Cefpodoxime	0.125–>32.0	4.0	>32.0
Cefuroxime	0.06–>32.0	8.0	>32.0
Clindamycin	2.0–>16.0	8.0	>16.0
Metronidazole	0.25–4.0	1.0	4.0
All fusobacteria (56/31)			
WY-49605	0.015–4.0	0.25	1.0
Amoxicillin	0.125–>256.0	4.0	256.0
Amoxicillin-clavulanate	0.125–32.0	0.5	8.0
Imipenem	0.015–0.5	0.03	0.25
Ciprofloxacin	0.25–16.0	2.0	16.0
Cefaclor	0.06–>32.0	1.0	>32.0
Cefpodoxime	0.06–>32.0	1.0	>32.0
Cefuroxime	0.06–>32.0	1.0	>32.0
Clindamycin	0.125–>16.0	0.5	>16.0
Metronidazole	0.125–4.0	1.0	4.0
Peptostreptococci[b] (55/0)			
WY-49605	0.015–2.0	0.125	1.0
Amoxicillin	0.125–128.0	2.0	8.0
Amoxicillin-clavulanate	0.125–64.0	1.0	4.0
Imipenem	0.015–0.25	0.015	0.125
Ciprofloxacin	0.25–8.0	1.0	4.0
Cefaclor	0.06–32.0	0.5	16.0
Cefpodoxime	0.06–32.0	0.5	16.0
Cefuroxime	0.06–32.0	0.5	8.0
Clindamycin	0.125–2.0	0.5	2.0
Metronidazole	0.25–>16.0	2.0	4.0
Propionibacteria[c] (19/0)			
WY-49605	0.03–2.0	0.125	0.5
Amoxicillin	0.25–128.0	1.0	16.0
Amoxicillin-clavulanate	0.125–64.0	0.5	8.0
Imipenem	0.015–0.25	0.015	0.125
Ciprofloxacin	0.25–2.0	0.25	2.0
Cefaclor	0.06–32.0	0.25	16.0
Cefpodoxime	0.06–16.0	0.25	4.0
Cefuroxime	0.06–8.0	0.06	2.0
Clindamycin	0.125–0.5	0.125	0.25
Metronidazole	16.0–>16.0	>16.0	>16.0
Other gram-positive anaerobic non-spore-forming rods[d] (30/0)			
WY-49605	0.015–4.0	0.125	2.0
Amoxicillin	0.125–128.0	4.0	16.0
Amoxicillin-clavulanate	0.125–32.0	4.0	16.0
Imipenem	0.015–0.5	0.015	0.5
Ciprofloxacin	0.25–8.0	1.0	2.0
Cefaclor	0.06–>32.0	1.0	32.0
Cefpodoxime	0.06–>32.0	1.0	16.0
Cefuroxime	0.06–16.0	0.25	8.0
Clindamycin	0.125–2.0	0.25	1.0
Metronidazole	16.0–>16.0	>16.0	>16.0
Clostridium perfringens (21/0)			
WY-49605	0.03–4.0	0.5	1.0
Amoxicillin	0.125–16.0	0.25	4.0
Amoxicillin-clavulanate	0.125–8.0	0.25	2.0
Imipenem	0.015–0.125	0.03	0.06
Ciprofloxacin	0.25–8.0	0.25	8.0
Cefaclor	0.06–>32.0	1.0	32.0
Cefpodoxime	0.06–>32.0	1.0	8.0
Cefuroxime	0.06–>32.0	2.0	8.0
Clindamycin	0.125–8.0	1.0	2.0
Metronidazole	0.5–4.0	1.0	4.0

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TABLE 1—*Continued*

Organism (no. of strains tested/no. of β-lactamase-positive strains) and antimicrobial agent	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Clostridium difficile (10/0)			
WY-49605	2.0–8.0	4.0	8.0
Amoxicillin	16.0–64.0	16.0	64.0
Amoxicillin-clavulanate	8.0–64.0	16.0	64.0
Imipenem	1.0–2.0	1.0	2.0
Ciprofloxacin	4.0–32.0	8.0	32.0
Cefaclor	16.0–>32.0	>32.0	>32.0
Cefpodoxime	16.0–>32.0	>32.0	>32.0
Cefuroxime	16.0–>32.0	>32.0	>32.0
Clindamycin	1.0–>16.0	4.0	>16.0
Metronidazole	0.25–8.0	2.0	4.0
Other clostridia[e] (16/0)			
WY-49605	0.125–2.0	0.25	2.0
Amoxicillin	0.5–32.0	8.0	16.0
Amoxicillin-clavulanate	0.25–16.0	4.0	8.0
Imipenem	0.015–2.0	0.06	0.5
Ciprofloxacin	0.25–16.0	4.0	8.0
Cefaclor	0.125–>32.0	8.0	>32.0
Cefpodoxime	0.125–>32.0	8.0	>32.0
Cefuroxime	0.125–>32.0	8.0	>32.0
Clindamycin	0.125–>16.0	8.0	>16.0
Metronidazole	0.25–>16.0	1.0	16.0
All strains (384/198)			
WY-49605	0.015–8.0	0.25	2.0
Amoxicillin	0.125–>256.0	8.0	>256.0
Amoxicillin-clavulanate	0.125–64.0	1.0	8.0
Imipenem	0.015–2.0	0.03	0.25
Ciprofloxacin	0.25–>64.0	2.0	16.0
Cefaclor	0.06–>32.0	8.0	>32.0
Cefpodoxime	0.06–>32.0	4.0	>32.0
Cefuroxime	0.06–>32.0	4.0	>32.0
Clindamycin	0.125–>16.0	0.5	8.0
Metronidazole	0.125–>16.0	2.0	16.0

[a] Eight *Bacteroides capillosus* strains, eight *Porphyromonas asaccharolytica* strains, nine *Prevotella oralis* strains, one *Bacteroides ureolyticus* strain, one *Prevotella loescheii* strain, and two *Prevotella oris* and *Prevotella buccae* strains.

[b] Two *Peptostreptococcus asaccharolyticus* strains, 14 *Peptostreptococcus magnus* strains, 1 *Peptostreptococcus prevotii* strain, 2 *Peptostreptococcus micros* strains, 6 *Peptostreptococcus anaerobius* strains, 21 *Peptostreptococcus tetradius* strains, 3 *Peptostreptococcus productus* strains, 3 *Peptostreptococcus* spp., and 3 *Streptococcus intermedius* strains.

[c] Eighteen *Propionibacterium acnes* strains and one *Propionibacterium avidum* strain.

[d] Four *Bifidobacterium* spp., 8 *Eubacterium* spp., 11 *Lactobacillus* spp., and 7 *Actinomyces* spp.

[e] Two *Clostridium ramosum* strains, two *Clostridium tertium* strains, one *Clostridium innocuum* strain, one *Clostridium sporogenes* strains, two *Clostridium butyricum* strains, two *Clostridium cadaveris* strains, two *Clostridium bifermentans* strains, one *Clostridium sordellii* strain, one *Clostridium septicum* strain, one *Clostridium histolyticum* strain, and one *Clostridium paraperfringens* strain.

blood agar plates (2). Throughout the study, strains were tested for purity by Gram staining and colonial morphology.

Susceptibility testing. Susceptibility powders of known potency were obtained as follows: WY-49605 from Wyeth-Ayerst Research, Radnor, Pa.; amoxicillin and clavulanate from SmithKline Beecham Laboratories, Philadelphia, Pa.; imipenem from Merck Research Laboratories, Rahway, N.J.; ciprofloxacin from Miles, Inc., West Haven, Conn.; cefaclor and cefuroxime from Eli Lilly and Co., Indianapolis, Ind.; clindamycin and cefpodoxime from The Upjohn Co., Kalamazoo, Mich.; and metronidazole from Searle, Inc., Skokie, Ill.) β-Lactamase testing was performed by the nitrocefin disk method (Cefinase; BBL Microbiology Systems, Cockeysville, Md.) (5). Agar dilution susceptibility testing was performed by the method recommended by the National Committee for Clinical Laboratory Standards (17), using Wilkins-Chalgren agar with 5% sterile defibrinated sheep blood for non-*B fragilis* group strains. Clavulanate was added to amoxicillin at a fixed concentration of 2.0 μg/ml. Standard quality control strains (17) were included with each run.

RESULTS

All 90 *B. fragilis* group strains, 88.5% of 87 non-*B. fragilis* group *Bacteroides* strains, *Prevotella* and *Porphyromonas* strains and 55.3% of 56 fusobacteria were β-lactamase positive by the nitrocefin disk method. By contrast, none of the 151 gram-positive strains tested produced this enzyme. Results of susceptibility testing are presented in Table 1. As can be seen, WY-49605 had an overall MIC at which 50% of the isolates are inhibited (MIC_{50}) of 0.25 μg/ml and an MIC at which 90% of the isolates are inhibited (MIC_{90}) of 2.0 μg/ml for all strains (range, 0.015 to 8.0 μg/ml). Only *Clostridium difficile* and lactobacilli were more resistant, with MIC_{50}s of 4.0 and 2.0 μg/ml, respectively, and MIC_{90}s of 8.0 and 2.0 μg/ml, respectively. By comparison, all other oral β-lactams tested were less active, with MIC_{50} and MIC_{90} results (in micrograms per milliliter), respectively, as follows: amoxicillin, 8.0 and >256; amoxicillin-clavulanate, 1.0 and 8.0; cefaclor, 8.0 and >32.0; cefpodoxime, 4.0 and >32.0; and cefuroxime, 4.0 and >32.0. Enhancement of amoxicillin MICs was observed by the addition of clavulanate in >95% of β-lactamase-producing strains but not in β-lactamase-negative strains. Imipenem was very active against all organisms (MIC_{50} of 0.03 μg/ml and MIC_{90} of 0.25 μg/ml), but only β-lactamase-negative strains showed significantly lower MICs to the three oral cephalosporins tested. In general, cefpodoxime and cefuroxime were more active than cefaclor against all strains. Among gram-positive strains, only non-*C. perfringens* clostridia, including *C. difficile*, showed significantly higher MICs to the three oral cephalosporins tested. Ciprofloxacin was less active, with an overall MIC_{50} of 2.0 μg/ml and MIC_{90} of 16.0 μg/ml. Clindamycin had an overall MIC_{50} of 0.5 μg/ml and an MIC_{90} of 8.0 μg/ml. Some members of the *B. fragilis* group, *Fusobacterium nucleatum*, *Fusobacterium varium*, and some *Clostridium* species yielded significant numbers of organisms with MICs of >2.0 μg/ml. Metronidazole had an MIC_{50} of 2.0 μg/ml and an MIC_{90} of 16.0 μg/ml against all strains. All gram-negative strains yielded MICs of ≤4.0 μg/ml; only gram-positive non-spore-forming anaerobic rods, some peptostreptococci, and some clostridia yielded MICs of >8.0 μg/ml.

Results of anaerobic gram-negative rods, broken down according to β-lactamase production, are presented in Table 2. As can be seen, all β-lactam MICs were significantly lower for strains which did not produce this enzyme. Higher clindamycin MICs in β-lactamase-positive fusobacteria reflect resistance in *F. varium* strains.

DISCUSSION

WY-49605 is a novel oral synthetic penem with a wide antibacterial spectrum which includes anaerobic bacteria as well as gram-positive and -negative pathogens (11, 14, 15, 18, 20–22, 24). Although lacking in activity against *Pseudomonas* species, WY-49605 is much more potent against staphylococci (methicillin susceptible), streptococci, and most gram-negative organisms (including *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Moraxella catarrhalis*) than other oral β-lactams

TABLE 2. Susceptibilities of β-lactamase-positive and -negative gram-negative anaerobic rods to antimicrobial agents

Bacteria	MIC_{50}/MIC_{90} (μg/ml) for strains		
	β-Lactamase-positive	β-Lactamase-negative	All
B. fragilis group			
WY-49605	0.5/2.0	—[a]	0.5/2.0
Amoxicillin	64.0/>256.0	—	64.0/>256.0
Amoxicillin-clavulanate	1.0/8.0	—	1.0/8.0
Imipenem	0.06/0.125	—	0.06/0.125
Ciprofloxacin	8.0/32.0	—	8.0/32.0
Cefaclor	32.0/>32.0	—	32.0/>32.0
Cefpodoxime	32.0/>32.0	—	32.0/>32.0
Cefuroxime	32.0/>32.0	—	32.0/>32.0
Clindamycin	0.25/4.0	—	0.25/4.0
Metronidazole	2.0/4.0	—	2.0/4.0
Non-*B. fragilis* group rods[b]			
WY-49605	0.25/1.0	0.03/0.06	0.125/1.0
Amoxicillin	32.0/>256.0	1.0/1.0	16.0/>256.0
Amoxicillin-clavulanate	2.0/8.0	0.5/1.0	1.0/8.0
Imipenem	0.06/0.5	0.015/0.06	0.06/0.5
Ciprofloxacin	4.0/16.0	8.0/16.0	4.0/16.0
Cefaclor	16.0/>32.0	0.125/8.0	8.0/>32.0
Cefpodoxime	8.0/>32.0	0.125/8.0	8.0/>32.0
Cefuroxime	8.0/32.0	0.25/8.0	8.0/>32.0
Clindamycin	0.5/1.0	0.25/1.0	0.25/1.0
Metronidazole	1.0/4.0	2.0/4.0	2.0/4.0
Fusobacteria			
WY-49605	0.5/2.0	0.06/0.5	0.25/1.0
Amoxicillin	32.0/>256.0	0.25/0.5	4.0/256.0
Amoxicillin-clavulanate	4.0/8.0	0.125/0.5	0.5/8.0
Imipenem	0.125/0.25	0.015/0.06	0.03/0.25
Ciprofloxacin	4.0/16.0	2.0/4.0	2.0/16.0
Cefaclor	8.0/>32.0	0.125/1.0	1.0/>32.0
Cefpodoxime	4.0/>32.0	0.25/1.0	1.0/>32.0
Cefuroxime	4.0/>32.0	0.25/1.0	1.0/>32.0
Clindamycin	2.0/>16.0	0.5/2.0	0.5/>16.0
Metronidazole	1.0/4.0	1.0/4.0	1.0/4.0
All strains			
WY-49605	0.25/2.0	0.06/0.5	0.25/2.0
Amoxicillin	64.0/256.0	0.25/1.0	8.0/>256.0
Amoxicillin-clavulanate	2.0/8.0	0.25/1.0	1.0/8.0
Imipenem	0.06/0.25	0.015/0.06	0.03/0.25
Ciprofloxacin	4.0/16.0	2.0/16.0	2.0/16.0
Cefaclor	32.0/>32.0	0.125/2.0	8.0/>32.0
Cefpodoxime	16.0/>32.0	0.125/4.0	4.0/>32.0
Cefuroxime	16.0/>32.0	0.25/2.0	4.0/>32.0
Clindamycin	0.5/8.0	0.25/2.0	0.5/8.0
Metronidazole	2.0/4.0	1.0/4.0	2.0/4.0

[a] —, no β-lactamase-negative strains isolated.
[b] Excluding fusobacteria.

such as cefaclor, cefixime, and amoxicillin (18). WY-49605 is equally active against strains carrying commonly encountered plasmid and chromosome-mediated β-lactamases. However, higher MICs have been encountered in some *Proteus* and *Morganella* species. Some strains of methicillin-resistant staphylococci are susceptible to WY-49605, although MICs are higher than those of methicillin-suscpetible strains. A noteworthy feature of WY-49605 is the narrow range of MICs, in contrast to the wider range of susceptibility of the newer oral cephalosporins (18).

The results of this study confirm the excellent activity of WY-49605 against all groups of anaerobes, except *C. difficile* and lactobacilli (24). Our results correspond well with those obtained by previous workers (18, 20, 21, 24). Previous studies have reported MIC_{90}s of between 3.13 and 8.0 μg/ml against *C. difficile* (20, 21, 24). MICs of WY-49605 were low against β-lactamase-positive as well as negative strains and were lower than those for all oral β-lactams tested in this study. Clindamycin had low MICs (<2.0 μg/ml) against most anaerobe groups but was less active against some members of the *B. fragilis* group, fusobacteria, and clostridial strains. Metronidazole had high MICs (>8.0 μg/ml) against most gram-positive non-spore-forming rods and some peptostreptococci and clostridia. Resistance to metronidazole in these anaerobe groups has been described previously (8). Imipenem, which had the lowest MICs against all groups, cannot be given orally and is also epileptogenic.

High peak levels in serum are obtained after the oral administration of WY-49605 to mice (10.2 μg/ml, 42.6% bioavailability) and dogs (39.0 μg/ml, 36.9% bioavailability) at doses of 20 mg/kg of body weight (1). Oral administration of 200 mg to rats has resulted in a maximum concentration of drug in serum of 21.0 μM, with an area under the curve of 16.9 μM/h (22). Initial results show good chemotherapeutic activity in experimental infections (18). WY-49605 has the potential for use in oral treatment of infections that are less predictably treatable with currently available oral agents and may fill in gaps in the spectra of clinidamycin and metronidazole. If the results of further pharmacokinetic and toxicologic studies are favorable, clinical studies of WY-49605 in therapy of anaerobic and mixed infections are indicated. Possible indications include ear, nose, and throat infections, dental infections, bite wounds, pelvic inflammatory disease, skin and soft tissue (including diabetic foot) infections, pulmonary infections, and chronic osteomyelitis. Additionally, oral therapy with WY-49605 could be used as a follow-up to parenteral therapy after hospital discharge in infections such as aspiration pneumonia and osteomyelitis.

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