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In Vitro Antianaerobic Activity of Ertapenem (MK-0826) Compared to Seven Other Compounds

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Ertapenem, imipenem, meropenem, ceftriaxone, piperacillin, piperacillin-tazobactam, clindamycin, and metronidazole were agar dilution MIC tested against 431 anaerobes. Imipenem, meropenem, and ertapenem were the most active β-lactams (MICs at which 50% of the strains are inhibited [MIC_{50}s], 0.125 to 0.25 μg/ml; MIC_{90}s, 1.0 to 2.0 μg/ml). Time-kill studies revealed that ertapenem at two times the MIC was bactericidal for 9 of 10 strains after 48 h. The kinetics for other β-lactams were similar to those of ertapenem.

Clinically isolated anaerobes are becoming more drug resistant (4, 6). Ertapenem (MK-0826) (1–3, 7, 11, 12) is a new, structurally unique, long-acting parenteral carbapenem. This study tested the antianaerobic activity of ertapenem by (i) comparing the MICs of ertapenem with those of imipenem, meropenem, ceftriaxone, piperacillin, piperacillin-tazobactam, clindamycin, and metronidazole against 431 anaerobes and (ii) testing the activities of all of the drugs against 10 anaerobes by time-kill studies.

The strains used were (i) 209 recent isolates from clinical trials with ertapenem obtained from Merck, Inc. (Rahway, N.J.) in Merck protocols 004, 016, 017, and 023 and (ii) 222 recent clinical isolates from our collection of species not included in the first group. All strains were isolated within 2 years of this study and were identified by standard methodology (10). Agar dilution MIC tests were performed on 431 strains, and time-kill assays were performed on 10 organisms.

β-Lactamase testing was done by nitrocefin disk (Cefinase; BBL Microbiology Systems, Cockeysville, Md.) (4). Agar dilution MIC tests were done as recommended by the National Committee for Clinical Laboratory Standards (5), using brucella agar (Difco) with 5% sterile defibrinated sheep blood and inocula of 10^5 CFU/spot. Tazobactam was combined with piperacillin at a fixed concentration of 4.0 μg/ml. For the 10 strains tested by time-kill (see Table 2), the microdilution MIC tests were done according to the recommendations of the National Committee for Clinical Laboratory Standards (5), using brucella broth (Difco) with 5% sterile defibrinated horse blood. Trays were inoculated with 10^6 CFU/ml.

Incubation of plates and trays was done in an anaerobic chamber (Coy Laboratory Products) in 80% N_2–10% H_2–10% CO_2. Standard quality control strains (*Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC 43055) were included with each run.

Time-kill testing was done as described previously (8, 9). Inocula were prepared inside the chamber by suspending five colonies from brucella blood agar plates in a tube containing 5 ml of prereduced brucella broth (Difco). A 100-μl aliquot was delivered by syringe into each vial containing 2.9 ml of prereduced brucella broth with 5% laked horse blood cells, 5 μg of hemin/ml, 1 μg of vitamin K_1/ml, and 1 ml of antibiotic dilution (prepared in prereduced brucella broth). All preparations and dilutions were prepared in the chamber. The vials were removed from the chamber and incubated for 48 h in a shaking water bath at 35°C (8, 9). For metronidazole, where thorough prereduction is necessary, 200 μl of Oxyrase (Mansfield, Ohio) solution was added (8, 9). The antibiotic ranges were MIC, two times the MIC, and four times the MIC.

One antibiotic-free growth control was used in each experiment. Aliquots containing 100 μl of diluted inoculum were added, with a final inoculum of 10^6 to 10^7 CFU/ml. The suspensions were incubated at 35°C in a shaking water bath, and viability counts (8, 9) were performed at 0, 6, 12, 24, and 48 h, with the plates incubated for 48 h inside the chamber. Data were analyzed by expressing viable counts as $\log_{10}$ CFU per milliliter higher or lower than the original inoculum at zero hour. Bacteriostatic activity was defined as 0 to <3 $\Delta\log_{10}$ CFU/ml, and bactericidal activity was defined as ≥ 3 $\Delta\log_{10}$ CFU/ml at each time period compared to zero hour. Drug carryover was minimized by dilution as described previously (8, 9). Kill kinetics data were analyzed by the Fisher exact test.

β-Lactamase was detected in 124 of 133 (93.2%) of the *B. fragilis* group, 55 of 80 (68.8%) *Prevotella-Porphyromonas* strains, and 5 of 41 (12.2%) fusobacteria. All gram-positive strains were β-lactamase negative. The results of agar dilution MIC testing are presented in Table 1. Imipenem, meropenem, and ertapenem were the most active β-lactams, with MICs at which 50% of the strains were inhibited (MIC_{50}s) of 0.125, 0.125, and 0.25 μg/ml and MIC_{90}s of 1.0, 1.0, and 2.0 μg/ml, respectively. Ertapenem, at ≤4.0 μg/ml, inhibited 95.8% of all 431 anaerobes tested. The only strains consistently ertapenem resistant (for which the MICs were >16.0 μg/ml) were lactobacilli (β-lactamase negative), which are rare human pathogens. Ceftriaxone and piperacillin were active against only β-lactamase-negative strains, while piperacillin-tazobactam

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TABLE 1. Agar dilution MICs against 431 strains

Strain and drug	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Bacteroides fragilis (47/47)[a]			
Ertapenem	0.125–>16.0	0.25	2.0
Imipenem	0.03–>8.0	0.25	1.0
Meropenem	0.125–>8.0	0.125	0.5
Ceftriaxone	4.0–>64.0	64.0	64.0
Piperacillin	2.0–>128.0	16.0	>128.0
Piperacillin-tazobactam	≤0.125–>128.0	1.0	4.0
Clindamycin	0.125–>32.0	2.0	>32.0
Metronidazole	0.5–4.0	1.0	2.0
Bacteroides thetaiotaomicron (33/30)			
Ertapenem	0.06–2.0	1.0	1.0
Imipenem	0.125–4.0	0.25	0.5
Meropenem	0.25–0.5	0.25	0.5
Ceftriaxone	64.0–>64.0	>64.0	>64.0
Piperacillin	32.0–>128.0	64.0	128.0
Piperacillin-tazobactam	1.0–32.0	8.0	32.0
Clindamycin	0.5–>32.0	4.0	16.0
Metronidazole	0.5–4.0	2.0	2.0
Bacteroides ovatus (17/17)			
Ertapenem	0.5–8.0	1.0	1.0
Imipenem	0.125–1.0	0.25	0.5
Meropenem	0.25–2.0	0.5	0.5
Ceftriaxone	32.0–>64.0	>64.0	>64.0
Piperacillin	16.0–>128.0	32.0	>128.0
Piperacillin-tazobactam	2.0–8.0	4.0	8.0
Clindamycin	2.0–>32.0	4.0	>32.0
Metronidazole	0.5–2.0	2.0	2.0
Bacteroides distasonis (10/5)			
Ertapenem	0.5–2.0	1.0	2.0
Imipenem	0.125–2.0	0.5	1.0
Meropenem	0.125–1.0	0.25	0.5
Ceftriaxone	2.0–>64.0	32.0	>64.0
Piperacillin	8.0–>128.0	64.0	>128.0
Piperacillin-tazobactam	2.0–32.0	4.0	8.0
Clindamycin	0.25–>32.0	8.0	16.0
Metronidazole	1.0–2.0	1.0	2.0
Bacteroides vulgatus (11/11)			
Ertapenem	0.125–4.0	0.125	2.0
Imipenem	0.25–4.0	0.5	4.0
Meropenem	0.25–4.0	0.25	1.0
Ceftriaxone	8.0–>64.0	16.0	>64.0
Piperacillin	8.0–>128.0	16.0	>128.0
Piperacillin-tazobactam	2.0–16.0	4.0	16.0
Clindamycin	0.03–>32.0	0.5	2.0
Metronidazole	0.5–2.0	1.0	2.0
Miscellaneous *Bacteroides fragilis* group[b] (15/14)			
Ertapenem	0.06–2.0	1.0	1.0
Imipenem	0.06–1.0	0.25	0.5
Meropenem	0.06–0.5	0.25	0.5
Ceftriaxone	0.25–>64.0	32.0	>64.0
Piperacillin	1.0–>128.0	32.0	>128.0
Piperacillin-tazobactam	≤0.125–16.0	2.0	8.0
Clindamycin	0.06–>32.0	4.0	>32.0
Metronidazole	0.25–4.0	1.0	2.0
All *Bacteroides fragilis* group (133/124)			
Ertapenem	0.06–>16.0	0.5	2.0
Imipenem	0.03–>8.0	0.25	1.0
Meropenem	0.06–>8.0	0.25	0.5
Ceftriaxone	0.25–>64.0	64.0	>64.0
Piperacillin	1.0–>128.0	32.0	>128.0
Piperacillin-tazobactam	≤0.125–>128.0	4.0	16.0
Clindamycin	0.03–>32.0	2.0	>32.0
Metronidazole	0.25–4.0	1.0	2.0
Prevotella bivia (30/24)			
Ertapenem	0.125–0.5	0.25	0.5
Imipenem	≤0.016–0.125	0.06	0.06
Meropenem	0.06–0.5	0.06	0.125
Ceftriaxone	0.25–>64.0	8.0	64.0
Piperacillin	1.0–128.0	8.0	64.0
Piperacillin-tazobactam	≤0.125–0.25	≤0.125	≤0.125
Clindamycin	≤0.016–0.06	0.03	0.06
Metronidazole	0.5–8.0	4.0	4.0
Prevotella corporis (10/3)			
Ertapenem	0.016–0.125	0.03	0.125
Imipenem	≤0.016–0.06	0.03	0.06
Meropenem	0.008–0.125	0.06	0.06
Ceftriaxone	≤0.125–32.0	≤0.125	16.0
Piperacillin	0.25–64.0	0.5	16.0
Piperacillin-tazobactam	≤0.125–0.25	≤0.125	≤0.125
Clindamycin	≤0.016–32.0	≤0.016	0.03
Metronidazole	≤0.125–1.0	0.5	1.0
Prevotella melaninogenica (10/9)			
Ertapenem	0.06–0.5	0.125	0.25
Imipenem	≤0.016–0.03	0.03	0.03
Meropenem	0.125–0.06	0.03	0.06
Ceftriaxone	≤0.125–64.0	1.0	32.0
Piperacillin	1.0–64.0	4.0	32.0
Piperacillin-tazobactam	≤0.125–≤0.125	≤0.125	≤0.125
Clindamycin	≤0.016–≤0.016	≤0.016	≤0.016
Metronidazole	0.5–1.0	0.5	1.0
Prevotella intermedia (10/6)			
Ertapenem	0.03–0.125	0.06	0.125
Imipenem	≤0.016–0.06	0.03	0.06
Meropenem	0.03–0.06	0.06	0.06
Ceftriaxone	≤0.125–32.0	2.0	8.0
Piperacillin	0.25–32.0	8.0	32.0
Piperacillin-tazobactam	≤0.125–≤0.125	≤0.125	≤0.125
Clindamycin	≤0.016–≤0.016	≤0.016	≤0.016
Metronidazole	0.25–1.0	0.5	1.0
Miscellaneous strains[c] (20/13)			
Ertapenem	0.008–0.5	0.125	0.5
Imipenem	≤0.016–0.125	0.06	0.125
Meropenem	0.008–0.25	0.125	0.25
Ceftriaxone	≤0.125–64.0	1.0	64.0
Piperacillin	≤0.125–128.0	4.0	128.0
Piperacillin-tazobactam	≤0.125–≤0.125	≤0.125	≤0.125
Clindamycin	≤0.016–0.03	≤0.016	0.03
Metronidazole	≤0.125–4.0	2.0	4.0
Prevotella-Porphyromonas (80/55)			
Ertapenem	0.008–0.5	0.125	0.5
Imipenem	≤0.016–0.125	0.03	0.125
Meropenem	0.008–0.5	0.06	0.125
Ceftriaxone	≤0.125–>64.0	4.0	64.0
Piperacillin	≤0.125–128.0	8.0	64.0
Piperacillin-tazobactam	≤0.125–0.25	≤0.125	≤0.125
Clindamycin	≤0.016–32.0	≤0.016	0.03
Metronidazole	≤0.125–8.0	2.0	4.0
Fusobacterium necrophorum (10/0)			
Ertapenem	≤0.004–0.016	≤0.004	0.008
Imipenem	≤0.016–0.03	≤0.016	≤0.016
Meropenem	≤0.008–0.016	≤0.008	0.016
Ceftriaxone	≤0.125–≤0.125	≤0.125	≤0.125
Piperacillin	≤0.125–≤0.125	≤0.125	≤0.125
Piperacillin-tazobactam	≤0.125–≤0.125	≤0.125	≤0.125
Clindamycin	0.03–0.06	0.06	0.06
Metronidazole	≤0.125–1.0	0.25	0.5

Continued on following page

TABLE 1—*Continued*

Strain and drug	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Fusobacterium nucleatum (10/1)			
Ertapenem	≤0.004–2.0	0.5	2.0
Imipenem	≤0.016–0.25	0.03	0.06
Meropenem	≤0.008–1.0	0.25	1.0
Ceftriaxone	≤0.125–4.0	1.0	2.0
Piperacillin	≤0.125–>128.0	≤0.125	0.25
Piperacillin-tazobactam	≤0.125–≤0.125	≤0.125	≤0.125
Clindamycin	0.03–0.125	0.06	0.125
Metronidazole	≤0.125–0.5	≤0.125	0.25
Fusobacterium mortiferum (11/2)			
Ertapenem	0.03–0.5	0.125	0.25
Imipenem	0.25–1.0	0.5	1.0
Meropenem	0.06–0.5	0.25	0.5
Ceftriaxone	32.0–>64.0	>64.0	>64.0
Piperacillin	0.25–>128.0	1.0	>128.0
Piperacillin-tazobactam	0.25–64.0	0.5	1.0
Clindamycin	0.06–0.125	0.125	0.125
Metronidazole	≤0.125–0.5	0.25	0.5
Fusobacterium varium (10/2)			
Ertapenem	0.06–8.0	0.125	1.0
Imipenem	0.5–2.0	0.5	1.0
Meropenem	0.06–8.0	0.125	8.0
Ceftriaxone	≤0.125–>64.0	4.0	16.0
Piperacillin	2.0–>128.0	16.0	64.0
Piperacillin-tazobactam	1.0–>128.0	8.0	16.0
Clindamycin	1.0–16.0	8.0	16.0
Metronidazole	0.25–2.0	0.5	0.5
Fusobacteria (41/5)			
Ertapenem	≤0.004–8.0	0.06	1.0
Imipenem	≤0.016–2.0	0.25	1.0
Meropenem	≤0.008–8.0	0.125	1.0
Ceftriaxone	≤0.125–>64.0	2.0	>64.0
Piperacillin	≤0.125–>128.0	0.25	64.0
Piperacillin-tazobactam	≤0.125–>128.0	0.25	8.0
Clindamycin	0.03–16.0	0.06	8.0
Metronidazole	≤0.125–2.0	0.25	0.5
Peptostreptococci[d] (53/0)			
Ertapenem	≤0.004–4.0	0.125	1.0
Imipenem	≤0.016–2.0	0.03	0.5
Meropenem	≤0.008–4.0	0.06	0.5
Ceftriaxone	≤0.125–32.0	0.5	16.0
Piperacillin	≤0.125–32.0	0.25	2.0
Piperacillin-tazobactam	≤0.125–16.0	≤0.125	2.0
Clindamycin	0.03–>32.0	0.25	4.0
Metronidazole	≤0.125–>16.0	1.0	2.0
Propionibacterium spp. (21/0)			
Ertapenem	0.06–0.5	0.25	0.5
Imipenem	≤0.016–0.03	0.03	0.03
Meropenem	0.03–0.5	0.25	0.5
Ceftriaxone	≤0.125–1.0	0.5	0.5
Piperacillin	0.5–2.0	1.0	2.0
Piperacillin-tazobactam	≤0.125–2.0	1.0	2.0
Clindamycin	0.06–0.25	0.125	0.125
Metronidazole	>16.0–>16.0	>16.0	>16.0
Eubacterium spp. (16/0)			
Ertapenem	0.06–2.0	1.0	1.0
Imipenem	≤0.016–0.5	0.5	0.5
Meropenem	0.06–4.0	0.25	0.5
Ceftriaxone	0.25–>64.0	32.0	>64.0
Piperacillin	0.25–32.0	16.0	32.0
Piperacillin-tazobactam	≤0.125–32.0	16.0	16.0
Clindamycin	0.03–>32.0	0.5	4.0
Metronidazole	0.25–>16.0	0.5	1.0
Lactobacillus spp. (11/0)			
Ertapenem	0.06–>16.0	16.0	>16.0
Imipenem	0.03–4.0	2.0	4.0
Meropenem	0.03–>8.0	8.0	>8.0
Ceftriaxone	1.0–>64.0	64.0	>64.0
Piperacillin	1.0–8.0	2.0	8.0
Piperacillin-tazobactam	1.0–4.0	2.0	4.0
Clindamycin	0.03–4.0	0.5	4.0
Metronidazole	1.0–>16.0	>16.0	>16.0
Other gram-positive nonspore-forming rods[e] (16/0)			
Ertapenem	0.03–2.0	0.25	1.0
Imipenem	≤0.016–0.5	0.25	0.25
Meropenem	0.03–1.0	0.125	0.5
Ceftriaxone	≤0.125–8.0	0.5	2.0
Piperacillin	≤0.125–4.0	0.5	2.0
Piperacillin-tazobactam	≤0.125–4.0	0.5	2.0
Clindamycin	≤0.016–16.0	0.06	4.0
Metronidazole	0.5–>16.0	>16.0	>16.0
Clostridium perfringens (22/0)			
Ertapenem	0.008–0.25	0.06	0.125
Imipenem	≤0.016–0.25	0.06	0.125
Meropenem	≤0.008–0.125	0.016	0.03
Ceftriaxone	0.25–16.0	2.0	8.0
Piperacillin	≤0.125–2.0	0.25	1.0
Piperacillin-tazobactam	≤0.125–1.0	0.25	0.5
Clindamycin	0.125–>32.0	2.0	4.0
Metronidazole	0.125–2.0	1.0	2.0
Clostridium difficile (10/0)			
Ertapenem	4.0–8.0	4.0	8.0
Imipenem	2.0–4.0	2.0	4.0
Meropenem	2.0–4.0	2.0	4.0
Ceftriaxone	32.0–>64.0	32.0	>64.0
Piperacillin	8.0–32.0	16.0	32.0
Piperacillin-tazobactam	8.0–32.0	8.0	16.0
Clindamycin	2.0–>32.0	4.0	>32.0
Metronidazole	0.25–0.5	0.25	0.25
Other clostridia[f] (28/0)			
Ertapenem	0.008–4.0	0.5	4.0
Imipenem	0.06–4.0	0.5	2.0
Meropenem	0.016–2.0	0.25	2.0
Ceftriaxone	0.25–>64.0	4.0	16.0
Piperacillin	0.25–16.0	1.0	16.0
Piperacillin-tazobactam	≤0.125–16.0	0.5	4.0
Clindamycin	0.06–>32.0	2.0	16.0
Metronidazole	≤0.125–2.0	1.0	1.0
All strains (431/184)			
Ertapenem	≤0.004–>16.0	0.25	2.0
Imipenem	≤0.016–>8.0	0.125	1.0
Meropenem	≤0.008–>8.0	0.125	1.0
Ceftriaxone	≤0.125–>64.0	16.0	>64.0
Piperacillin	≤0.125–>128.0	4.0	64.0
Piperacillin-tazobactam	≤0.125–>128.0	0.5	16.0
Clindamycin	≤0.016–>32.0	0.5	16.0
Metronidazole	≤0.125–>16.0	1.0	>16.0

[a] Number of strains tested/number of strains β-lactamase positive.

[b] *Bacteroides caccae* (2), *Bacteroides merdae* (1), *Bacteroides splanchnicus* (3), *Bacteroides stercoris* (7), and *Bacteroides fragilis* group (2).

[c] *Prevotella oris* (1), *Prevotella denticola* (1), *Prevotella buccae* (8), *Prevotella disiens* (8), and *Porphyromonas asaccharolytica* (2).

[d] *Peptostreptococcus asaccharolyticus* (9), *Peptostreptococcus magnus* (15), *Peptostreptococcus anaerobius* (13), *Peptostreptococcus micros* (4), *Peptostreptococcus prevotii* (1), and *Peptostreptococcus tetradius* (11).

[e] *Actinomyces* spp. (6) and *Bifidobacterium* spp. (8).

[f] *Clostridium tertium* (1), *Clostridium bifermentans* (2), *Clostridium sordellii* (6), *Clostridium cadaveris* (1), *Clostridium baratii* (1), *Clostridium butyricum* (1), *Clostridium chlostridioforme* (1), *Clostridium hastiforme* (1), *Clostridium innocuum* (3), *Clostridium paraputrificum* (1), *Clostridium ramosum* (3), and *Clostridium* spp. (7).

TABLE 2. Time-kill assay results[a]

Drug and concn	No. of strains											
	6 h			12 h			24 h			48 h		
	−1[b]	−2[b]	−3[b]	−1	−2	−3	−1	−2	−3	−1	−2	−3
Ertapenem												
4× MIC	10	7	5	10	10	7	10	9	8	10	9	9
2× MIC	10	7	4	10	9	6	10	9	8	10	9	9
MIC	10	6	2	10	9	6	9	8	7	9	8	8
Imipenem												
4× MIC	9	7	5	10	10	7	10	10	8	10	10	9
2× MIC	9	7	5	10	8	7	10	10	8	10	10	9
MIC	9	7	4	10	8	7	10	10	8	10	10	9
Meropenem												
4× MIC	9	7	1	10	9	6	10	10	10	10	10	10
2× MIC	8	4	0	10	9	5	10	10	9	10	10	10
MIC	8	4	0	10	7	3	8	8	4	6	6	5
Ceftriaxone												
4× MIC	10	7	4	10	9	8	10	10	9	10	10	10
2× MIC	10	6	3	10	9	7	10	10	9	10	10	10
MIC	9	5	0	10	8	6	9	9	8	9	8	8
Piperacillin												
4× MIC	9	8	6	10	8	8	10	9	8	10	9	9
2× MIC	9	8	4	10	8	8	10	9	8	10	9	9
MIC	9	7	2	10	8	6	10	9	7	9	8	8
Piperacillin-tazobactam												
4× MIC	9	6	3	10	9	7	10	9	9	10	9	9
2× MIC	8	4	2	10	9	7	10	9	9	10	9	9
MIC	7	2	1	10	6	4	10	8	7	9	6	5
Clindamycin												
4× MIC	5[c]	1[c]	0[c]	9	5[c]	1[c]	10	9	4	10	10	8
2× MIC	5[c]	1[c]	0	9	5	1[c]	10	8	4	10	10	8
MIC	5[c]	0[c]	0	8	4[c]	1[c]	7	4	1	6	6	4
Metronidazole												
4× MIC	10	9	7	10	10	9	10	10	9	10	10	9
2× MIC	10	9	4	10	10	9	10	9	8	10	8	7
MIC	10	7	2	10	10	7	10	7	7	9	5	5

[a] Strains tested: B. fragilis (2), *B. thetaiotaomicron* (1), *P. bivia* (1), *Prevotella disiens* (1), *F. nucleatum* (1), *Fusobacterium mortiferum* (1), *Peptostreptocccus asaccharolyticus* (1), *C. perfringens* (1), and *C. difficile* (1).

[b] Log_{10} CFU per milliliter decrease in colony count compared to time zero at indicated time (−1 = 90% killing; −2 = 99% killing; −3 = 99.9% killing).

[c] Proportions of strains at different extents of killing are significantly less ($P < 0.05$) than observed with ertapenem.

was active against β-lactamase-positive and -negative strains. Clindamycin resistance occurred in some *B. fragilis* group strains and clostridia, and metronidazole resistance was found in anaerobic gram-positive rods and a few peptostreptococci.

Microdilution MIC results for the 10 strains used for time-kill studies (Table 2) were within 1 dilution of the MIC_{50}s (Table 1), except for one *B. fragilis* strain (clindamycin MIC, 0.5 μg/ml), one *B. fragilis* strain (piperacillin-tazobactam MIC, 0.25 μg/ml); one *B. thetaiotaomicron* strain (piperacillin-tazobactam MIC, 2.0 μg/ml); one *Prevotella bivia* strain (meropenem MIC, 0.25 μg/ml; ceftriaxone and piperacillin MICs, 32.0 μg/ml), one *Prevotella intermedia* strain (ceftriaxone MIC, 16.0 μg/ml), one *Fusobacterium nucleatum* strain (ertapenem and meropenem MICs, 0.008 μg/ml; ceftriaxone MIC, 0.125 μg/ml), and one *Clostridium perfringens* strain (piperacillin MIC, 1.0 μg/ml; metronidazole MIC, 4.0 μg/ml).

Time-kill tests (Table 2) revealed that ertapenem at two times the MIC was bactericidal (99.9% killing) for 9 of 10 strains after 48 h, with 90% killing of all 10 strains after 24 h at two times the MIC. The one strain not killed by ertapenem after 48 h at two times the MIC was a *Clostridium difficile* strain, also not killed by imipenem but killed by meropenem at two times the MIC after 48 h. Kinetics for all β-lactams relative to the MIC were similar to those of ertapenem, with bactericidal activity at two times the MIC after 48 h. Clindamycin was bactericidal against 8 strains after 48 h at two times the MIC, with 90% killing of all 10 strains after 24 h at two times the MIC. Metronidazole was bactericidal against eight strains at two times the MIC after 24 h and against seven strains after 48 h. Clindamycin killed strains significantly more slowly ($P < 0.05$) than ertapenem at 6 and 12 h; no other statistically significant differences were found.

Ertapenem is a new long-acting 1-β-*methyl* carbapenem antibiotic with antibacterial activities comparable or superior to

those of established agents against gram-positive and -negative organisms. Ertapenem has an antibacterial spectrum including common aerobic and anaerobic bacteria and organisms with extended-spectrum β-lactamases. Advantageous pharmacokinetics, including an extended half-life at 32 β phase and improved stability to renal DHP-1, support development of this compound as a single once-daily-dosing agent in moderate-to-severe community-acquired and mixed infections (2, 7, 11).

Wexler et al. (12) reported MICs similar to ours against 363 anaerobes, with ≥98% of strains susceptible to ertapenem, imipenem, and meropenem. In another recent study, the ertapenem MICs were similar to those reported here: ertapenem was uniformly active against all 1,001 isolates with the exception of 12 of 61 (20%) *Bilophila wadsworthia* strains, 3 lactobacilli, and 1 strain of *Acidaminococcus fermentans* (3). Our study confirms the antianaerobic activity of ertapenem by MIC and time-kill tests.

In summary, ertapenem showed low MICs and good kill kinetics against a wide variety of anaerobes. These data, together with the its spectrum of activity against aerobes and its favorable pharmacokinetics, make ertapenem a promising choice for treatment of mixed aerobic-anaerobic infections. Clinical studies will be necessary to validate these findings.

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