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In Vitro Activity of Biapenem (L-627), a New Carbapenem, against Anaerobes

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We tested 441 clinical strains of anaerobes by using a broth microdilution method to determine the in vitro activity of biapenem for comparison with those of other agents. Biapenem had activity comparable to those of imipenem and meropenem against all groups of anaerobes with MICs for 90% of the strains tested of 0.06 to 2 μg/ml. Against the *Bacteroides fragilis* group, biapenem was more active than ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin, cefoxitin, cefotaxime, and ceftriaxone. Biapenem was also active against all of the *B. capillosus*, *Prevotella*, *Clostridium*, and *Eubacterium* strains and anaerobic cocci tested. Against all of the anaerobes tested, biapenem was 32- and 4-fold more active than clindamycin and metronidazole, respectively. These data indicate broad-spectrum activity by biapenem against anaerobes.

The predominant mechanism of β-lactam resistance among anaerobes is production of β-lactamases. Most of the β-lactamases studied are characterized as cephalosporinases, particularly among the *Bacteroides* spp. (12). However, other anaerobes have β-lactamases which are characterized as penicillinases (14). Production of these enzymes is primarily chromosomally mediated, but resistance to cefoxitin by β-lactamase production has also been shown to be plasmid mediated and transferable (4).

Imipenem, a broad-spectrum carbapenem, is highly resistant to most types of β-lactamases from both aerobes and anaerobes (2). Two exceptions are type I, chromosomally mediated β-lactamases from aerobic, gram-negative bacilli and the metallo-containing β-lactamases of anaerobes (3). Moreover, in clinical use imipenem must be combined with cilastatin to prevent breakdown of the former by renal dehydropeptidase-I (7, 8). Biapenem (L-627; LJC 10,627) is a new carbapenem agent that has a structure similar to that of imipenem but differs by the presence of a methyl group in the 1-beta position. Addition of the methyl group confers resistance to the action of dehydropeptidase-I (5). The present study compared the in vitro activity of biapenem with those of imipenem, meropenem, and other agents against clinical isolates of anaerobes.

We tested 441 clinical strains of various anaerobes. The test group comprised the following: *Bacteroides fragilis* group, 339 strains; *B. capillosus*, 10 strains; *Prevotella bivia*, 15 strains; *P. disiens*, 13 strains; *Eubacterium* spp., 18 strains; *Clostridium*, spp., 14 strains; *Peptostreptococcus* spp., 17 strains; *Veillonella parvula*, 15 strains. Each strain was identified by using selective media, biochemical profiles, and gas-liquid chromatography (6, 15). β-Lactamase production was detected by using a nitrocephin assay (Cefinase; BBL Microbiology Systems).

Standard powders for susceptibility testing were provided by the following manufacturers: ampicillin and sulbactam, Pfizer Inc., New York, N.Y.; ticarcillin and clavulanate, SmithKline Beecham Laboratories, Philadelphia, Pa.; piperacillin and biapenem, Lederle Laboratories, Pearl River, N.Y.; metronidazole, Searle, Skokie, Ill.; clindamycin, The Upjohn Co., Kalamazoo, Mich.; cefotaxime, Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; meropenem, Stuart Pharmaceuticals, Wilmington, Del.; ceftriaxone, Roche Inc., Nutley, N.J.; cefoxitin and imipenem, Merck Sharp & Dohme, West Point, Pa. All standard powders were stored desiccated at −20°C until use.

Each strain was tested with a broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (10). Serial twofold dilutions of each antimicrobial agent (or combination) were prepared with Anaerobe Broth MIC (Difco) within a dilution scheme of 0.015 to 128 μg/ml. When combining ampicillin with sulbactam, a 2:1 ratio was used. Clavulanate was tested at a constant concentration of 2 μg/ml when combined with serial twofold dilutions of ticarcillin. The inoculum was prepared by suspending colonies from an overnight blood agar plate in 5 ml of prereduced Anaerobe Broth MIC equivalent to a density equal to a no. 1 McFarland standard and further diluted to give a final inoculum of 10^5 CFU per well (10^6 CFU/ml). All plates were incubated for 48 h at 35°C anaerobically and then read. The MIC was determined as the lowest concentration of each antimicrobial agent which inhibited visible growth of the test isolate. With each susceptibility run, quality control was performed with *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *E. lentum* ATCC 43055.

All strains of the *B. fragilis* group, *B. capillosus*, *P. bivia*, and *P. disiens* were β-lactamase producers, whereas all of the other strains tested were β-lactamase nonproducers.

Table 1 compares the activity of biapenem with those of the other antimicrobial agents tested. Biapenem was highly active against all of the anaerobe test groups, inhibiting 98.6% of the isolates tested at ≤1 μg/ml. By comparison, biapenem was equally as active as imipenem and meropenem. Against most of the various species of the *B. fragilis* group, biapenem was 8- to 32-fold more active than ampicillin-sulbactam and ticarcillin-clavulanate and 4- to 16-fold more active against *Prevotella* spp. and *B. capillosus*. The highest levels of resistance to all three carbapenem compounds were seen among strains of *Clostridium* spp. and *Peptostreptococcus* spp., with MICs for 90% of the strains tested of 1 to 2 μg/ml. Biapenem was more active than ampicillin-sulbactam and ticarcillin-clavulanate against most *Eubacterium* spp., *Clostridium* spp., and anaerobic cocci. Biapenem was more active than metronidazole against most groups of anaerobes, especially the anaerobic gram-negative bacilli. Biapenem was more active than cefoxitin, cefotaxime, ceftriaxone, and piperacillin against all of the

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TABLE 1. Comparison of the activities of biapenem and other antimicrobial agents against clinical strains of anaerobes

Organism(s) (no. of strains tested) and drug(s)[a]	MIC (μg/ml)[b]				% Resistant[c]
	Range	Mode	50%	90%	
B. fragilis group (339)					
Biapenem	0.12–2	0.12	0.12	0.25	0, 0, 0
Imipenem	0.12–2	0.12	0.12	0.5	0, 0, 0
Meropenem	0.06–32	0.12	0.12	0.5	0, 0, 0
Ampicillin-sulbactam	0.06–32	0.5	1	4	2, 0.3, 0
Ticarcillin-clavulanate	0.06–64	0.06	0.25	2	0.3, 0, 0
Piperacillin	0.12–128	2	8	64	17, 9, 0
Cefoxitin	0.5–128	8	8	32	21, 8, 2
Cefotaxime	0.25–128	4	4	128	28, 15, 11
Ceftriaxone	0.06–128	4	8	128	40, 32, 14
Clindamycin	0.03–16	0.5	1	16	27, 16, 12
Metronidazole	0.06–2	0.5	0.5	1	0, 0, 0
B. fragilis (176)					
Biapenem	0.12–2	0.12	0.12	0.25	0, 0, 0
Imipenem	0.12–2	0.12	0.12	0.5	0, 0, 0
Meropenem	0.06–2	0.12	0.12	0.5	0, 0, 0
Ampicillin-sulbactam	0.06–16	0.5	0.5	4	0, 0, 0
Ticarcillin-clavulanate	0.06–16	0.12	0.12	2	0, 0, 0
Piperacillin	0.12–128	2	4	64	15, 7, 0
Cefoxitin	0.5–128	8	8	32	11, 6, 1
Cefotaxime	0.25–128	4	4	128	18, 14, 12
Ceftriaxone	0.06–128	4	4	128	21, 18, 12
Clindamycin	0.03–16	0.5	0.5	16	10, 9, 9
Metronidazole	0.12–2	0.5	0.5	1	0, 0, 0
B. thetaiotaomicron (50)					
Biapenem	0.12–1	0.25	0.25	0.25	0, 0, 0
Imipenem	0.12–2	0.12	0.12	0.5	0, 0, 0
Meropenem	0.06–2	0.25	0.25	0.25	0, 0, 0
Ampicillin-sulbactam	0.25–32	1	1	4	2, 2, 0
Ticarcillin-clavulanate	0.06–16	0.5	0.5	2	0, 0, 0
Piperacillin	0.5–128	16	16	64	12, 8, 0
Cefoxitin	1–64	16	16	32	44, 8, 0
Cefotaxime	0.25–128	32	16	64	50, 14, 8
Ceftriaxone	0.25–128	64	64	128	78, 74, 18
Clindamycin	0.5–16	4	4	8	60, 26, 10
Metronidazole	0.12–2	0.5	0.5	1	0, 0, 0
B. distasonis (32)					
Biapenem	0.12–1	0.12	0.25	0.5	0, 0, 0
Imipenem	0.12–1	0.12	0.25	0.5	0, 0, 0
Meropenem	0.06–1	0.12	0.12	0.5	0, 0, 0
Ampicillin-sulbactam	0.5–16	0.5	2	8	0, 0, 0
Ticarcillin-clavulanate	0.06–64	8	4	16	3, 0, 0
Piperacillin	1–128	4	8	128	28, 16, 0
Cefoxitin	8–128	8	16	32	34, 9, 3
Cefotaxime	0.5–128	0.5	2	64	28, 19, 9
Ceftriaxone	0.5–128	1	4	128	31, 28, 16
Clindamycin	0.03–16	4	2	8	44, 12, 6
Metronidazole	0.06–2	0.5	0.5	1	0, 0, 0
B. ovatus (35)					
Biapenem	0.12–1	0.25	0.25	0.25	0, 0, 0
Imipenem	0.12–1	0.12	0.12	0.25	0, 0, 0
Meropenem	0.06–2	0.25	0.25	0.25	0, 0, 0
Ampicillin-sulbactam	0.12–16	1	1	8	0, 0, 0
Ticarcillin-clavulanate	0.06–16	0.5	0.5	4	0, 0, 0
Piperacillin	0.5–128	8	16	128	20, 14, 0
Cefoxitin	8–128	16	16	64	29, 11, 6
Cefotaxime	0.25–128	16	16	128	49, 17, 11
Ceftriaxone	0.12–128	64	64	128	91, 57, 17
Clindamycin	0.25–16	16	4	16	69, 43, 37
Metronidazole	0.25–2	0.5	0.5	1	0, 0, 0
B. vulgatus (33)					
Biapenem	0.12–1	0.25	0.25	0.5	0, 0, 0
Imipenem	0.12–1	0.12	0.12	0.5	0, 0, 0

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TABLE 1—*Continued*

Organism(s) (no. of strains tested) and drug(s)[a]	MIC (μg/ml)[b]				% Resistant[c]
	Range	Mode	50%	90%	
Meropenem	0.06–1	0.12	0.25	0.5	0, 0, 0
Ampicillin-sulbactam	0.25–8	0.5	1	4	0, 0, 0
Ticarcillin-clavulanate	0.06–0.5	0.06	0.06	0.25	0, 0, 0
Piperacillin	0.5–128	4	4	64	11, 9, 0
Cefoxitin	0.5–128	4	4	64	21, 15, 6
Cefotaxime	0.25–128	1	2	32	15, 9, 9
Ceftriaxone	0.5–128	4	4	128	24, 15, 12
Clindamycin	0.03–16	0.06	0.25	16	15, 15, 15
Metronidazole	0.12–1	0.25	0.25	0.5	0, 0, 0
B. uniformis (13)					
Biapenem	0.12–0.5	0.12	0.25	0.25	0, 0, 0
Imipenem	0.12–0.5	0.12	0.12	0.25	0, 0, 0
Meropenem	0.06–0.25	0.12	0.12	0.25	0, 0, 0
Ampicillin-sulbactam	0.5–4	0.5	2	4	0, 0, 0
Ticarcillin-clavulanate	0.12–0.5	0.5	0.5	0.5	0, 0, 0
Piperacillin	4–128	4	16	128	23, 15, 0
Cefoxitin	1–64	2	4	64	23, 15, 0
Cefotaxime	4–128	4	16	128	44, 31, 15
Ceftriaxone	4–128	32	32	128	69, 46, 23
Clindamycin	0.03–4	1	1	4	23, 0, 0
Metronidazole	0.12–1	0.25	0.25	1	0, 0, 0
B. capillosus (15)					
Biapenem	0.06–0.12	0.12	0.12	0.12	0, 0, 0
Imipenem	0.06–0.12	0.12	0.12	0.12	0, 0, 0
Meropenem	0.03–0.12	0.06	0.06	0.06	0, 0, 0
Ampicillin-sulbactam	0.25–2	1	1	1	0, 0, 0
Ticarcillin-clavulanate	0.03–0.06	0.06	0.06	0.06	0, 0, 0
Piperacillin	1–16	2	2	8	0, 0, 0
Cefoxitin	1–16	2	2	8	0, 0, 0
Cefotaxime	0.12–0.5	0.5	0.25	0.5	0, 0, 0
Ceftriaxone	0.5–8	0.5	1	8	0, 0, 0
Clindamycin	0.01–0.03	0.02	0.02	0.02	0, 0, 0
Metronidazole	0.5–2	1	1	2	0, 0, 0
P. bivia (15)					
Biapenem	0.12	0.12	0.12	0.12	0, 0, 0
Imipenem	0.12	0.12	0.12	0.12	0, 0, 0
Meropenem	0.06–0.12	0.06	0.06	0.12	0, 0, 0
Ampicillin-sulbactam	0.06–2	2	1	2	0, 0, 0
Ticarcillin-clavulanate	0.06	0.06	0.06	0.06	0, 0, 0
Piperacillin	0.12–32	1	4	32	0, 0, 0
Cefoxitin	0.5–8	0.5	2	8	0, 0, 0
Cefotaxime	0.06–8	0.5	0.5	8	0, 0, 0
Ceftriaxone	0.06–32	1	2	16	7, 0, 0
Clindamycin	0.02–0.03	0.02	0.02	0.02	0, 0, 0
Metronidazole	0.25–8	1	1	2	0, 0, 0
P. disiens (13)					
Biapenem	0.06–0.12	0.12	0.12	0.12	0, 0, 0
Imipenem	0.06–0.12	0.12	0.12	0.12	0, 0, 0
Meropenem	0.03–0.06	0.06	0.06	0.06	0, 0, 0
Ampicillin-sulbactam	0.03–1	0.5	0.25	0.5	0, 0, 0
Ticarcillin-clavulanate	0.03–0.06	0.06	0.06	0.06	0, 0, 0
Piperacillin	0.06–16	1	2	8	0, 0, 0
Cefoxitin	0.25–4	0.5	1	4	0, 0, 0
Cefotaxime	0.03–4	0.25	0.25	0.5	0, 0, 0
Ceftriaxone	0.06–8	0.5	1	8	0, 0, 0
Clindamycin	0.01–0.02	0.01	0.01	0.02	0, 0, 0
Metronidazole	0.03–4	1	1	2	0, 0, 0
Eubacterium spp. (18)[d]					
Biapenem	0.12–0.5	0.12	0.12	0.12	0, 0, 0
Imipenem	0.12–0.5	0.12	0.12	0.5	0, 0, 0
Meropenem	0.06–0.25	0.25	0.25	0.25	0, 0, 0
Ampicillin-sulbactam	0.06–1	0.06	0.25	1	0, 0, 0

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TABLE 1—*Continued*

Organism(s) (no. of strains tested) and drug(s)[a]	MIC (μg/ml)[b]				% Resistant[c]
	Range	Mode	50%	90%	
Ticarcillin-clavulanate	0.06–32	16	16	32	0, 0, 0
Piperacillin	0.12–16	0.12	2	16	0, 0, 0
Cefoxitin	0.25–16	8	8	16	0, 0, 0
Cefotaxime	0.06–128	128	0.5	128	50, 50, 39
Ceftriaxone	0.06–128	128	4	128	50, 50, 50
Clindamycin	0.02–16	0.12	1	16	11, 11, 11
Metronidazole	0.03–32	0.25	0.25	1	6, 6, 6
Clostridium spp. (14)[e]					
Biapenem	0.12–1	0.12	0.12	1	0, 0, 0
Imipenem	0.12–2	0.12	0.12	2	0, 0, 0
Meropenem	0.06–1	0.06	0.06	1	0, 0, 0
Ampicillin-sulbactam	0.06–1	0.06	0.06	0.25	0, 0, 0
Ticarcillin-clavulanate	0.06–16	0.06	0.12	16	0, 0, 0
Piperacillin	0.12–64	0.12	0.25	2	7, 0, 0
Cefoxitin	0.25–128	0.25	1	64	21, 21, 7
Cefotaxime	0.06–32	4	4	8	7, 0, 0
Ceftriaxone	0.06–8	8	1	8	0, 0, 0
Clindamycin	0.03–16	0.03	0.25	8	14, 14, 7
Metronidazole	0.03–2	1	0.5	2	0, 0, 0
Peptostreptococcus spp. (17)[f]					
Biapenem	0.12–2	0.12	0.12	2	0, 0, 0
Imipenem	0.12–1	0.12	0.12	2	0, 0, 0
Meropenem	0.06–2	0.06	0.12	2	0, 0, 0
Ampicillin-sulbactam	0.06–8	0.06	0.12	8	0, 0, 0
Ticarcillin-clavulanate	0.06–128	0.06	1	128	24, 12, 0
Piperacillin	0.12–8	0.12	0.12	4	0, 0, 0
Cefoxitin	0.12–8	8	0.5	8	0, 0, 0
Cefotaxime	0.06–8	0.06	0.25	4	0, 0, 0
Ceftriaxone	0.06–8	4	1	8	0, 0, 0
Clindamycin	0.02–1	0.06	0.06	1	0, 0, 0
Metronidazole	0.02–2	1	0.5	1	0, 0, 0
Veillonella parvula (10)					
Biapenem	0.06	0.06	0.06	0.06	0, 0, 0
Imipenem	0.06–0.12	0.06	0.06	0.12	0, 0, 0
Meropenem	0.03	0.03	0.03	0.03	0, 0, 0
Ampicillin-sulbactam	0.03–0.25	0.03	0.03	0.25	0, 0, 0
Ticarcillin-clavulanate	0.03–8	0.03	0.12	8	0, 0, 0
Piperacillin	0.06–16	0.06	0.06	16	0, 0, 0
Cefoxitin	0.06–1	0.06	0.12	1	0, 0, 0
Cefotaxime	0.03–0.5	0.03	0.03	0.5	0, 0, 0
Ceftriaxone	0.03–0.5	0.03	0.03	0.5	0, 0, 0
Clindamycin	0.03–0.06	0.03	0.03	0.06	0, 0, 0
Metronidazole	0.06–2	0.25	0.25	2	0, 0, 0

[a] The ampicillin-sulbactam ratio was 2:1. Clavulanate was used at 2 μg/ml.
[b] 50% and 90%, MICs for 50 and 90% of strains tested.
[c] Percent resistance results are expressed as the breakpoint (underlined) and 1 dilution above and below the breakpoint. The following resistance breakpoint values (in micrograms per milliliter), as recommended by the National Committee for Clinical Laboratory Standards (10) or the manufacturer, were used: clindamycin, ≥8; biapenem, meropenem, and imipenem, ≥16; ampicillin-sulbactam and metronidazole, ≥32; cefoxitin, cefotaxime, and ceftriaxone, ≥64; piperacillin and ticarcillin-clavulanate, ≥128.
[d] Includes 13 *E. lentum*, 4 *E. linosum*, and 1 *E. aerofaciens* strains.
[e] Includes four *C. perfringens*, one *C. cadaveris*, one *C. innocuum*, two *C. ramosum*, two *C. butyricum*, one *C. septicum*, and one *C. subterminale* strains.
[f] Includes 15 *P. anaerobius* and 2 *P. asaccharolyticus* strains.

groups of anaerobes. Compared with clindamycin, biapenem was more active against the *B. fragilis* group, *Eubacterium* spp., and *Clostridium* spp. but less active against *Prevotella* spp., *B. capillosus*, and *Peptostreptococcus* spp.

Weiss et al. (16) reported a mean peak concentration of biapenem in plasma of approximately 37 μg/ml in volunteers who received 600-mg intravenous infusions three times a day. Comparison of these levels in plasma with the MICs for 90% of the strains tested indicates achievable in vivo levels 37 to 617 times higher than the in vitro concentrations needed to inhibit the various groups of anaerobes.

This study indicates that biapenem is highly active in vitro against all of the clinical isolates tested and shows activity comparable to those of imipenem and meropenem. Catchpole et al. (2) reported good activity of biapenem against strains of *B. fragilis* and *Peptostreptococcus* spp., although biapenem was eightfold less active against *B. fragilis* than in our study. Nord et al. (11) also recently reported good in vitro activity of

biapenem against a variety of anaerobes. By comparison, their results obtained with strains of *B. fragilis*, *Bacteroides* spp., and *Prevotella* spp. were similar to ours. However, their strains of anaerobic gram-positive cocci were slightly more susceptible than the *Peptostreptococcus* spp. in our study. Our results are identical to those of Malanoski et al. (9) and Sader and Jones (13), showing good activity against *B. fragilis* isolates. These biapenem results are also similar to those of Applebaum et al. (1) obtained with *Bacteroides*, *Prevotella*, *Peptostreptococcus*, and *Clostridium* strains. These data indicate wide-spectrum antianaerobic activity of biapenem. Additional pharmacologic and clinical studies are needed to assess the role of biapenem in anaerobic infections.

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