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In Vitro Activities of Ertapenem (MK-0826) against Clinical Bacterial Isolates from 11 North American Medical Centers

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This study compared the in vitro activities of the new long-half-life carbapenem ertapenem (also known as MK-0826 and L-749,345) with those of imipenem, amoxicillin-clavulanate, and ciprofloxacin against 5,558 recent clinical isolates from 11 North American medical centers. We confirmed the greater activity of ertapenem than of imipenem against the *Enterobacteriaceae* and the greater activity of imipenem against pseudomonads and gram-positive bacteria.

Ertapenem (also known as MK-0826 and L-749,345) is a new long-half-life carbapenem with a broad spectrum of antimicrobial activity against both gram-positive and gram-negative bacteria (1–4, 7). Preliminary pharmacokinetic studies indicate that ertapenem has a prolonged half-life (half-life at β phase of 4.9 ± 0.7 h) sufficient to permit once-a-day dosing (2, 8). This long half-life is largely due to its high protein binding of >95% (8). Ertapenem MICs found in the presence of serum were no more than eightfold higher than in standard tests (I. Pelak, S. Gerckens, P. M. Scott, C. Gill, C. Pacholok, L. Lynch, K. Dorso, J. Kohler, D. Shungu, and H. Kropp, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F119, p. 120, 1996). In animal studies the high protein binding had no apparent deleterious effect on ertapenem's in vivo efficacy (2). Peak levels in plasma of human volunteers following a 1.0-g intravenous dose were >100 μg/ml (8). The drug is currently undergoing clinical trials. The present study was designed to assess the in vitro activity of ertapenem in comparison with those of imipenem, amoxicillin-clavulanate, and ciprofloxacin against clinical isolates from 11 North American medical centers.

For these studies, 5,558 bacterial isolates were obtained from the 11 North American medical centers listed at the end of this paper. These isolates included 2,019 nonfastidious gram-negative bacteria, 540 fastidious gram-negative bacteria, 2,789 gram-positive isolates, and 210 anaerobes. Each center was requested to collect consecutive isolates that were deemed clinically significant during late winter to early spring of 1999. For each species, collection continued until a predefined target number of isolates was obtained or until the collection period ended. Multiple isolates from one patient were not included so that the consecutive isolates truly represent bacterial pathogens being encountered at that time. All isolates submitted for testing were identified by each contributing laboratory using their own standard methods. All susceptibility tests were performed at the Clinical Microbiology Institute, Wilsonville, Oreg. The species and numbers of each species tested are listed in Table 1.

Ertapenem and imipenem were provided as standardized powders by Merck Research Laboratories, Rahway, N.J. Ciprofloxacin, amoxicillin-clavulanate, and ampicillin were obtained from their respective U.S. manufacturers or other commercial source. All aerobic bacteria were evaluated by broth microdilution methods as outlined by the NCCLS (5). Microdilution panels were prepared by PML Microbiologicals, Wilsonville, Oreg., and stored at −70°C until used. The cation-adjusted Mueller-Hinton broth was supplemented with ca. 3% lysed horse blood when necessary for growth (e.g., streptococci). Haemophilus test medium was used for testing *Haemophilus* species. Concentrations of drugs tested were serial twofold dilutions ranging from 16 to 0.008 μg/ml for ertapenem, imipenem, and ciprofloxacin; 32 to 0.03 μg/ml for amoxicillin-clavulanate; and 4.0 to 0.03 for ampicillin (fastidious gram-negative isolates only). Anaerobic bacteria were tested by the agar dilution method recommended by the NCCLS (6), using Brucella blood agar supplemented with vitamin K_1 (1.0 μg/ml) and hemin (5 μg/ml) and using an inoculum of ca. 10^5 CFU per spot.

On each day of testing, colony counts were performed on the bacterial suspension in the growth control wells of two randomly selected microdilution trays to ensure an inoculum density of approximately 5×10^5 CFU/ml. Standard control strains that were included with each test run were those that were appropriate for the species of clinical isolates being tested.

Table 1 summarizes the antimicrobial activities of ertapenem and three comparison agents against 5,558 strains of clinical bacterial isolates. Ertapenem was more active against all species of *Enterobacteriaceae* than imipenem. Ertapenem MICs were generally 10 to 20 times lower than those of imipenem for most species and were over 100 times lower for some species of the tribe *Proteeae*. Against *Pseudomonas aeruginosa* and related species, both drugs were less active than against the *Enterobacteriaceae,* but imipenem was more active than ertapenem. Amoxicillin-clavulanate was the least active of the four drugs tested against nonfastidious gram-negative bacteria. Ciprofloxacin MICs were generally slightly higher than those of ertapenem and lower than those of imipenem for *Enterobacteriaceae,* and for most species of non-*Enterobacteriaceae* they were lower than those of the other drugs tested.

Ertapenem was active against gram-positive bacteria other than enterococci and oxacillin-resistant staphylococci (Table 1). Imipenem was more potent than ertapenem against nearly

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TABLE 1. Susceptibilities of 5,558 clinical isolates to ertapenem and three comparator drugs

Microorganism(s) (no. of isolates) and antimicrobial agent[b]	MIC (μg/ml)		
	Range	50%	90%
Acinetobacter spp.[a] (86)			
Ertapenem	0.06–>16	4.0	16
Imipenem	≤0.008–>16	0.25	2.0
Amox-clav	0.06–>32	16	>32
Ciprofloxacin	≤0.008–>16	1.0	>16
Aeromonas spp.[c] (21)			
Ertapenem	0.03–1.0	0.06	0.25
Imipenem	0.25–4.0	0.5	2.0
Amox-clav	16–>32	32	>32
Ciprofloxacin	≤0.008–1.0	0.016	0.12
Burkholderia cepacia (13)			
Ertapenem	4.0–>16	8.0	>16
Imipenem	8.0–>16	16	>16
Amox-clav	32–32	>32	>32
Ciprofloxacin	1.0–>16	4.0	>16
Citrobacter spp.[d] (216)			
Ertapenem	≤0.008–4.0	≤0.008	0.25
Imipenem	0.06–2.0	0.5	1.0
Amox-clav	2.0–>32	16	>32
Ciprofloxacin	≤0.008–>16	0.03	1.0
Enterobacter spp.[e] (239)			
Ertapenem	≤0.008–>16	0.03	0.5
Imipenem	0.12–>16	1.0	2.0
Amox-clav	1.0–>32	>32	>32
Ciprofloxacin	≤0.008–>16	0.03	1.0
Escherichia coli (254)			
Ertapenem	≤0.008–0.5	≤0.008	0.016
Imipenem	0.06–2.0	0.12	0.25
Amox-clav	1.0–>32	8.0	32
Ciprofloxacin	≤0.008–>16	0.03	0.06
Klebsiella spp.[f] (359)			
Ertapenem	≤0.008–>16	≤0.008	0.03
Imipenem	0.06–>16	0.25	0.5
Amox-clav	1.0–>32	4.0	16
Ciprofloxacin	≤0.008–>16	0.06	1.0
Pasteurella multocida (22)			
Ertapenem	≤0.008–0.03	0.016	0.03
Imipenem	0.03–0.5	0.25	0.5
Amox-clav	0.06–0.5	0.25	0.5
Ciprofloxacin	≤0.008–0.06	≤0.008	0.016
Proteeae[g] (284)			
Ertapenem	≤0.008–4.0	0.016	0.03
Imipenem	0.016–16	4.0	4.0
Amox-clav	0.5–>32	16	>32
Ciprofloxacin	≤0.008–>16	0.06	>16
Pseudomonas aeruginosa (161)			
Ertapenem	0.12–>16	8.0	>16
Imipenem	0.25–>16	2.0	8.0
Amox-clav	32–>32	>32	>32
Ciprofloxacin	0.03–>16	0.5	>16
Pseudomonas spp.[h] (29)			
Ertapenem	≤0.008–>16	8.0	>16
Imipenem	0.12–>16	1.0	>16
Amox-clav	1.0–>32	>32	>32
Ciprofloxacin	≤0.008–>16	0.25	1.0
Salmonella spp.[i] (112)			
Ertapenem	≤0.008–0.06	≤0.008	≤0.008
Imipenem	0.12–1.0	0.25	0.5
Amox-clav	1.0–>32	1.0	16
Ciprofloxacin	≤0.008–0.12	0.016	0.03
Serratia marcescens (110)			
Ertapenem	≤0.008–>16	0.03	0.12
Imipenem	0.12–>16	1.0	2.0
Amox-clav	4.0–>32	>32	>32
Ciprofloxacin	≤0.008–>16	0.25	4.0
Shigella spp.[j] (37)			
Ertapenem	≤0.008	≤0.008	≤0.008
Imipenem	0.06–0.5	0.25	0.25
Amox-clav	4.0–32	16	32
Ciprofloxacin	≤0.008–0.25	≤0.008	0.06
Stenotrophomonas maltophilia (54)			
Ertapenem	1.0–>16	>16	>16
Imipenem	8.0–>16	>16	>16
Amox-clav	4.0–>32	>32	>32
Ciprofloxacin	1.0–>16	8.0	>16
Miscellaneous gram-negative bacteria[k] (22)			
Ertapenem	≤0.008–>16	0.03	4.0
Imipenem	0.06–>16	1.0	4.0
Amox-clav	0.12–>32	8.0	32
Ciprofloxacin	≤0.008–>16	0.5	4.0
Haemophilus spp.[l] (332)			
Ertapenem	≤0.008–0.5	0.03	0.06
Imipenem	≤0.008–2.0	0.5	1.0
Ampicillin	0.12–>4.0	0.5	>4.0
Ciprofloxacin	≤0.008–16	0.016	0.03
Moraxella catarrhalis (181)			
Ertapenem	≤0.008–0.25	≤0.008	0.016
Imipenem	≤0.008–1.0	0.12	0.25
Ampicillin	≤0.03–1.0	0.25	0.5
Ciprofloxacin	≤0.008–0.5	0.016	0.03
Neisseria meningitidis (27)			
Ertapenem	≤0.008–0.03	≤0.008	0.016
Imipenem	0.03–1.0	0.25	0.5
Ampicillin	0.12–0.5	0.12	0.25
Ciprofloxacin	≤0.008	≤0.008	≤0.008
Corynebacterium spp.[m] (29)			
Ertapenem	≤0.008–>16	0.5	>16
Imipenem	≤0.008–>16	1.0	>16
Amox-clav	≤0.03–>32	0.5	>32
Ciprofloxacin	0.5–>16	>16	>16
Enterococcus faecalis[n] (387)			
Ertapenem	0.06–>16	8.0	>16
Imipenem	0.03–>16	2.0	16
Amox-clav	0.06–>32	0.5	1.0
Ciprofloxacin	0.25–>16	1.0	>16
Enterococcus faecium[o] (140)			
Ertapenem	0.12–>16	>16	>16
Imipenem	0.25–>16	>16	>16
Amox-clav	0.06–>32	>32	>32
Ciprofloxacin	0.25–>16	>16	>16
Enterococcus spp.[p] (other) (23)			
Ertapenem	0.5–>16	8.0	>16
Imipenem	0.03–>16	4.0	>16
Amox-clav	0.12–>32	1.0	32
Ciprofloxacin	0.06–>16	2.0	>16
Staphylococcus aureus			
Oxacillin susceptible (375)			
Ertapenem	0.03–>16	0.12	0.25
Imipenem	0.016–>16	0.016	0.03
Amox-clav	0.06–8.0	1.0	1.0
Ciprofloxacin	0.03–>16	0.25	0.5

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TABLE 1—*Continued*

Microorganism(s) (no. of isolates) and antimicrobial agent[b]	MIC (μg/ml)		
	Range	50%	90%
Oxacillin resistant (172)			
Ertapenem	0.12–>16	>16	>16
Imipenem	0.03–>16	16	>16
Amox-clav	0.12–>32	>32	>32
Ciprofloxacin	0.12–>16	>16	>16
Staphylococcus spp., coagulase negative Oxacillin susceptible (182)			
Ertapenem	0.03–4.0	0.12	0.5
Imipenem	≤0.008–1.0	0.016	0.06
Amox-clav	≤0.03–32	0.25	4.0
Ciprofloxacin	0.03–2.0	0.25	0.5
Oxacillin resistant (346)			
Ertapenem	0.06–>16	8.0	>16
Imipenem	≤0.008–>16	1.0	>16
Amox-clav	0.12–>32	32	>32
Ciprofloxacin	0.06–>16	8.0	>16
Streptococcus agalactiae (206)			
Ertapenem	0.016–0.25	0.06	0.06
Imipenem	≤0.008–0.06	0.016	0.03
Amox-clav	≤0.03–0.12	0.06	0.12
Ciprofloxacin	0.5–4.0	1.0	1.0
Streptococcus pneumoniae			
Penicillin susceptible (373)			
Ertapenem	≤0.008–0.06	0.016	0.03
Imipenem	≤0.008–0.03	≤0.008	0.016
Amox-clav	0.06–0.25	0.06	0.06
Ciprofloxacin	0.5–16	1.0	2.0
Penicillin intermediate (93)			
Ertapenem	≤0.008–1.0	0.25	0.5
Imipenem	≤0.008–0.5	0.12	0.25
Amox-clav	≤0.03–2.0	0.5	1.0
Ciprofloxacin	0.5–16	1.0	2.0
Penicillin resistant (110)			
Ertapenem	0.12–4.0	1.0	2.0
Imipenem	0.12–2.0	0.25	1.0
Amox-clav	0.12–8.0	1.0	8.0
Ciprofloxacin	0.5–8.0	1.0	2.0
Streptococcus pyogenes (238)			
Ertapenem	≤0.008–0.25	≤0.008	0.016
Imipenem	≤0.008–0.06	≤0.008	≤0.008
Amox-clav	≤0.03–0.12	≤0.03	≤0.03
Ciprofloxacin	0.12–2.0	0.5	1.0
Streptococcus spp.[q] (other) (77)			
Ertapenem	≤0.008–4.0	0.12	0.5
Imipenem	≤0.008–2.0	0.016	0.12
Amox-clav	≤0.03–8.0	≤0.03	0.25
Ciprofloxacin	0.016–16	0.5	8.0
Miscellaneous gram-positive bacteria[r] (38)			
Ertapenem	≤0.008–>16	0.25	2.0
Imipenem	≤0.008–4.0	0.03	0.12
Amox-clav	0.03–>32	0.12	0.5
Ciprofloxacin	0.03–>16	1.0	4.0
Bacteroides fragilis (56)			
Ertapenem	0.016–4.0	0.25	1.0
Imipenem	≤0.008–2.0	0.12	0.5
Bacteroides spp.[s] (64)			
Ertapenem	0.03–8.0	0.5	2.0
Imipenem	0.03–4.0	0.25	1.0
Clostridium perfringens (21)			
Ertapenem	≤0.008–0.12	0.06	0.06
Imipenem	0.03–0.5	0.06	0.12
Proprionibacterium acnes (21)			
Ertapenem	0.03–4.0	0.06	0.25
Imipenem	≤0.008–1.0	≤0.008	0.03
Miscellaneous anaerobes[t] (48)			
Ertapenem	≤0.008–4.0	0.12	0.5
Imipenem	≤0.008–2.0	0.06	0.25

[a] Species (no. of isolates): *A. anitratus* (12), *A. baumannii* (59), *A. haemolyticus* (8), and *A. lwoffii* (7).
[b] Amox-clav, amoxicillin-clavulanate.
[c] Species (no. of isolates) *A. caviae* (3), *A. hydrophila* (11), and *Aeromonas* spp. NOS (7).
[d] Species (no. of isolates): *C. amalonaticus* (8), *C. brackii* (1), *C. diversus* (18), *C. farmeri* (3), *C. freundii* (119), *C. koseri* (66), and *Citrobacter* spp. NOS (1).
[e] Species (no. of isolates): *E. aerogenes* (111), *E. agglomerans* (9), *E. asburiae* (1), *E. cancerogenus* (1), *E. cloacae* (112), *E. intermedius* (2), *E. sakasaki* (1), and *Enterobacter* spp. NOS (2).
[f] Species (no. of isolates): *K. ornitholytica* (1), *K. oxytoca* (103), and *K. pneumoniae* (255).
[g] Species (no. of isolates): *M. morganii* (94), *P. mirabilis* (113), *P. vulgaris* (25), *P. rettgeri* (18), and *P. stuartii* (34).
[h] Species (no. of isolates): *P. fluorescens/putida* group (22), *P. paucimobilis* (1), *P. stutzeri* (2), *P. vesiculare* (1), and *Pseudomonas* spp. NOS (3).
[i] Species (no. of isolates): *S. enterica* serovar Tyhi (3) and non-serovar Typhi salmonellae (109).
[j] Species (no. of isolates): *S. bovdii* (1), *S. flexneri* (7), *S. sonnei* (27), and *Shigella* spp. NOS (2).
[k] Species (no. of isolates): *Alcaligenes faecalis* (5), *Bordetella bronchiseptica* (1), *Brevundimonas vesicularis* (1), *Commamonas* spp. (1), *Flavobacterium breve* (1), *F. mengosepticum* (1), *Hafnia alvei* (2), *Pasteurella* spp. NOS (2), *Serratia liquefaciens* (1), *S. rubidaea* (1), *Shawanella putrefaciens* (1), and *Yersinia enterocolitica* (5).
[l] Species (no. of isolates): *H. aegypticus* (1), *H. aphrophilus* (3), *H. haemolyticus* (4), *H. influenzae* (233; 86 β-lactamase-positive), *H. parahaemolyticus* (1), and *H. parainfluenzae* (30).
[m] Species (no. of isolates): *C. afermentans* (1), *C. amycolatum* (1), *C. jeikeium* (7; resistant to all drugs), *C. pseudodiphtheriticum* (1), *C. striatum* (3), *C. ureolyticum* (3; resistant to all drugs), and *Corynebacterium* spp. NOS (13).
[n] Includes 10 vancomycin-resistant strains.
[o] Includes 90 vancomycin-resistant strains.
[p] Species (no. of isolates): *E. avium* (9), *E. casseliflavus* (3), *E. durans* (1), *E. gallinarum* (8), *E. raffinosus* (1), and *Enterococcus* spp. NOS (1).
[q] Species (no. of isolates): group C (5), group F (6), group G (21), *S. bovis* (6), *S. milleri* (13), *S. mitis* (2), *S. mutans* (2), *S. salivarius* (3), *S. sanguis* (4), and *S. viridans* NOS (15).
[r] Species (no. of isolates): *Aerococcus* spp. NOS (2), *A. urinae* (4), *Bacillus* spp. NOS (8), *Lactobacillus* spp. NOS (10), *Micrococcus* spp. NOS (13), and *L. monocytogenes* (1).
[s] Species (no. of isolates): *B. fragilis* group, NOS (9), *B. ovatus* (9), *B. thetaiotaomicron* (19), *B. uniformis* (11), *B. vulgatus* (5), and *Bacteroides* spp. NOS (11).
[t] Species (no. of isolates): *Actinomyces* spp. (9), *Bifidobacterium* spp. (2), *Clostridium* spp. NOS (9), *Eubacterium lentum* (2), *Fusobacterium* spp. (6), *Peptostreptococcus* spp. (10), *Prevotella* spp. (6), *Propionibacterium* spp. NOS (3), and *Veillonella parvula* (1).

all gram-positive species. The MICs of ertapenem and imipenem were higher for penicillin-resistant pneumococci (MICs at which 90% of the isolates tested were inhibited [MIC_{90}], 2.0 and 1.0 μg/ml) than against penicillin-susceptible pneumococci (MIC_{90}, 0.03 and 0.016 μg/ml). The geometric mean MICs of both carbapenems were 40-fold higher for penicillin-resistant pneumococci than for penicillin-susceptible strains. A similar difference in MICs was observed with amoxicillin-clavulanate,

but ciprofloxacin MICs were unaffected by penicillin susceptibility of pneumococci.

Fastidious gram-negative bacteria, except for ampicillin resistance of β-lactamase-producing *Haemophilus* spp., were highly susceptible to all four test drugs (Table 1). For *Haemophilus* spp., the MICs of ertapenem were 2- to 10-fold lower than those of imipenem. β-Lactamase production by *H. influenzae* had no perceptible effect on the MICs of either carbapenem or ciprofloxacin.

Virtually all anaerobic isolates tested were susceptible to ≤4.0 μg of both carbapenems per ml (Table 1). Against *Clostridium perfringens,* ertapenem was twice as active as imipenem, but against the other anaerobic bacteria, imipenem was more potent.

In summary, ertapenem was superior to the other study drugs in its potency against the *Enterobacteriaceae* but it had relatively little activity against *Pseudomonas* spp. Although ertapenem was active against most gram-positive cocci, imipenem was somewhat more potent. Both carbapenems had little activity against the enterococci, especially vancomycin-resistant strains. Anaerobic bacteria were also susceptible to both carbapenems even though imipenem was more potent than ertapenem. Because ertapenem may be given once a day and because of its potency against the *Enterobacteriaceae,* ertapenem might be useful in treating a variety of infections in humans.

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