Antipneumococcal Activity of Ertapenem (MK-0826) Compared to Those of Other Agents

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The activities of ertapenem (MK-0826) and eight other agents against a range of penicillin-susceptible and -resistant pneumococci were tested by determination of MICs by the microdilution method and by the time-kill methodology. For 125 penicillin-susceptible, 74 penicillin-intermediate, and 86 penicillin-resistant pneumococci, the MICs at which 50% of isolates are inhibited (MIC₅₀s) and MIC₉₀s, as determined by the microdilution method, were as follows: for ertapenem, 0.016 and 0.03, 0.125 and 0.5, and 0.5 and 1.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for amoxicillin, ≤0.016 and 0.03, 0.25 and 1.0, and 2.0 and 2.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for cefprozil, 0.125 and 0.25, 1.0 and 8.0, and 16.0 and 16.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for cefepime, ≤0.016 and 0.06, 0.5 and 1.0, and 1.0 and 2.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for ceftriaxone, ≤0.016 and 0.06, 0.25 and 1.0, and 1.0 and 2.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for imipenem, ≤0.008 and ≤0.008, 0.03 and 0.25, and 0.25 and 0.25 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; for meropenem, ≤0.008 and 0.016, 0.125 and 0.5, and 0.5 and 1.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively; and for clarithromycin, 1.0 and >32.0, 1.0 and >32.0, and >32.0 µg/ml for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci, respectively. For 64 strains for which quinolone MICs were increased (ciprofloxacin MICs, ≥4.0 µg/ml), the MIC₉₀ of ertapenem was 1.0 µg/ml and the MIC₉₀s of the other β-lactams tested and clarithromycin were >32.0 µg/ml. Against four penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant strains, testing by the time-kill methodology showed that ertapenem at two times the MIC was bacteriostatic (99% killing) after 12 h and bactericidal (99.9% killing) against all strains by 24 h, with 90% killing of all strains at two times the MIC after 6 h. At the MIC, ertapenem was bacteriostatic against all strains tested after 24 h. Although the bactericidal activity of imipenem at the MIC after 24 h was significantly greater than that of ertapenem, the kinetics of the two drugs at two times the MIC were similar after 24 h. The killing kinetics of clarithromycin were slower than those of ertapenem and other agents, with clarithromycin at two times the MIC having bactericidal activity against seven of eight macrolide-susceptible strains after 24 h.

The prevalence of pneumococci resistant to penicillin G and other β-lactam and non-β-lactam compounds has increased worldwide at an alarming rate, including in the United States (1, 5, 6, 10, 11). Major foci of resistance presently include South Africa, Spain, Central and Eastern Europe, and parts of Asia (1, 10, 11). A recent survey in the United States showed that 50.4% of 1,476 clinically significant pneumococcal isolates were not susceptible to penicillin (12). Macrolide resistance was detected in 33% of isolates, including 5% of penicillin-susceptible strains, 37% of penicillin-intermediate strains, and 66% of penicillin-resistant strains. However, no quinolone-resistant strains were isolated (12). The problem of drug-resistant pneumococci is compounded by the ability of resistant clones to spread from country to country and from continent to continent (13, 14).

There is a need for agents that can be used to treat infections caused by penicillin-intermediate and -resistant pneumococci

(2, 5, 6). Therapeutic modalities include β-lactams, macrolides, and quinolones. Because of the mechanism of β-lactam resistance in pneumococci, the MICs of all β-lactams rise with those of penicillin G, and the clinical utility of an agent is dependent on its pharmacokinetics (10–12). The MICs of the available carbapenems are low relative to the MICs of penicillin, with imipenem having the lowest MICs, followed by meropenem (10, 11). Macrolide resistance has already been alluded to (12). Older quinolones such as ciprofloxacin and ofloxacin have moderate in vitro activities against pneumococci, with MICs clustering around the breakpoints, while newer quinolones such as levofloxacin, sparfloxacin, grepafloxacin, gatifloxacin, moxifloxacin, gemifloxacin, clinafloxacin, and sitafloxacin have lower MICs for pneumococci (4, 17, 20, 21, 23).

Ertapenem (MK-0826; L-749,345) is a new long-acting parenteral carbapenem (7, 8, 16, 22; M. L. van Ogtrop, D. Andes, and W. A. Craig, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 999, 1999; M. L. Van Ogtrop, D. Andes, and W. A. Craig, Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-48, 1998). The present study investigates the antipneumococcal activity of ertapenem by (i) determination by the microdilution method of the MICs of

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ertapenem, amoxicillin, cefprozil, cefotaxime, ceftriaxone, imipenem, meropenem, and clarithromycin for a spectrum of penicillin-susceptible and -resistant strains; (ii) determination by the microdilution method of the MICs of ertapenem, levofloxacin, sparfloxacin, grepafloxacin, gatifloxacin, and moxifloxacin as well as those of the other drugs listed above for pneumococci for which quinolone MICs are increased and for which the quinolone resistance mechanisms are known; and (iii) time-kill testing of β -lactams and macrolides against strains with various susceptibilities to β -lactams and macrolides.

MATERIALS AND METHODS

Bacteria. The quinolone-susceptible strains studied comprised 95 penicillin-susceptible strains (penicillin MICs, ≤ 0.06 $\mu\text{g/ml}$), 58 penicillin-intermediate strains (penicillin MICs, 0.125 to 1.0 $\mu\text{g/ml}$), and 68 penicillin-resistant strains (penicillin MICs, 2.0 to 16.0 $\mu\text{g/ml}$) (ciprofloxacin MICs were ≤ 2.0 $\mu\text{g/ml}$ for all strains). All susceptible strains and some intermediate and resistant strains were recently obtained in the United States. The remainder of the intermediate and resistant strains were isolated in South Africa, Spain, France, Central and Eastern Europe, and Korea. Additionally, 64 strains for which ciprofloxacin MICs were ≥ 4 $\mu\text{g/ml}$ (recently obtained from the United States and Europe) were selected. Of these, 30 were penicillin susceptible, 16 were penicillin intermediate, and 18 were penicillin resistant; and quinolone resistance mechanisms were known for all strains (4).

Antimicrobials and MIC testing. Ertapenem powder for susceptibility testing was obtained from Merck & Co., Inc., Rahway, N.J. The other antimicrobials used in the study were obtained from their respective manufacturers. Microdilution MICs were determined according to the recommendations of NCCLS (15) with cation-adjusted Mueller-Hinton broth and 5% lysed defibrinated horse blood. Standard quality control strains, including *Streptococcus pneumoniae* ATCC 49619, were included in each run. Because of the known instability of carbapenem, fresh aliquots of carbapenem powder were used in each run.

Testing for time-kill activities. The time-kill activities of the β -lactams and clarithromycin against four penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant strains were tested as described previously (19). Antibiotic concentrations were chosen to comprise 3 doubling dilutions above and 1 doubling dilution below the MIC. Growth controls with inoculum but no antibiotic were included with each experiment (19). The original inoculum was determined by using the untreated growth control. Only tubes containing an initial inoculum within the range of 5×10^5 to 5×10^6 CFU/ml were acceptable (19). As described above, fresh carbapenem powders were used in each test for time-kill activity. Viability counts of antibiotic-containing suspensions were performed at 0, 3, 6, 12, and 24 h, as described previously (19). Colony counts were performed for plates that yielded 30 to 300 colonies. The lower limit of sensitivity of colony counts was 300 CFU/ml (19).

The results of the time-kill assays were analyzed by determining the number of strains which yielded changes in counts of -1 , -2 , and $-3 \log_{10}$ CFU/ml at 3, 6, 12, and 24 h compared to the counts at 0 h. The antimicrobials were considered bactericidal if the lowest concentration tested reduced the original inoculum by $\geq 3 \log_{10}$ CFU/ml (99.9%) at each of the time periods and bacteriostatic if the lowest concentration tested reduced the inoculum by 0 to $<3 \log_{10}$ CFU/ml. The problem of bacterial carryover was addressed by dilution, as described previously (19). For testing of the time-kill activity of clarithromycin, only strains for which clarithromycin MICs were ≤ 0.03 $\mu\text{g/ml}$ were tested, while for testing of the time-kill activity of ciprofloxacin, the one strain for which the ciprofloxacin MIC was >64.0 $\mu\text{g/ml}$ was excluded.

Statistical analysis. The Fisher exact test was used to test for significant differences in the number of strains killed at each MIC and time period for all antibiotics tested.

RESULTS

The results of testing of the MICs for all 285 strains by the broth microdilution method are presented in Table 1. As can be seen, the MICs of all β -lactams rose with those of penicillin G; imipenem had the lowest MICs, followed by ertapenem and meropenem, ceftriaxone and cefepime, and amoxicillin and

TABLE 1. Microdilution MICs for all 285 strains tested

Drug and penicillin susceptibility ^a	MIC ($\mu\text{g/ml}$)		
	Range	MIC ₅₀	MIC ₉₀
Penicillin			
S	≤ 0.016 –0.06	≤ 0.016	0.06
I	0.125–1.0	0.25	1.0
R	2.0–4.0	2.0	4.0
Ertapenem			
S	≤ 0.008 –0.125	0.016	0.03
I	0.03–1.0	0.125	0.5
R	0.25–4.0	0.5	1.0
Amoxicillin			
S	≤ 0.016 –0.125	≤ 0.016	0.03
I	≤ 0.016 –2.0	0.25	1.0
R	0.5–8.0	2.0	2.0
Cefprozil			
S	≤ 0.06 –4.0	0.125	0.25
I	≤ 0.06 –16.0	1.0	8.0
R	2.0–32.0	16.0	16.0
Cefepime			
S	≤ 0.016 –1.0	≤ 0.016	0.06
I	0.03–4.0	0.5	1.0
R	0.5–4.0	1.0	2.0
Ceftriaxone			
S	≤ 0.016 –1.0	≤ 0.016	0.06
I	0.03–4.0	0.25	1.0
R	0.5–4.0	1.0	2.0
Imipenem			
S	≤ 0.008 –0.03	≤ 0.008	≤ 0.008
I	≤ 0.008 –0.5	0.03	0.25
R	0.125–1.0	0.25	0.25
Meropenem			
S	≤ 0.008 –0.06	≤ 0.008	0.016
I	≤ 0.008 –0.5	0.125	0.5
R	0.25–2.0	0.5	1.0
Clarithromycin			
S	≤ 0.03 – >32.0	1.0	>32.0
I	≤ 0.03 – >32.0	1.0	>32.0
R	≤ 0.03 – >32.0	>32.0	>32.0

^a S, susceptible; I, intermediate; R, resistant.

cefprozil. All strains were inhibited by ertapenem at ≤ 4.0 $\mu\text{g/ml}$, and 284 of 285 strains (99.7%) were inhibited by ertapenem at ≤ 2.0 $\mu\text{g/ml}$. Clarithromycin-resistant strains were seen mainly among the penicillin-intermediate and -resistant strains, but several macrolide-resistant strains were included in the penicillin-susceptible group (Table 1). When the results for the 221 strains for which ciprofloxacin MICs were ≤ 2.0 $\mu\text{g/ml}$ were analyzed separately (data not shown), no significant differences in β -lactam or macrolide MICs compared to those indicated in Table 1 were found.

When strains for which ciprofloxacin MICs were ≥ 4.0 $\mu\text{g/ml}$ were analyzed separately (Table 2), the results obtained for β -lactams and clarithromycin were similar to those obtained for all strains and presented in Table 1, while quinolone-resistant strains were found in the penicillin-susceptible as well as the non-penicillin-susceptible groups (Table 2). Additionally,

TABLE 2. Broth microdilution MICs for 64 quinolone-resistant pneumococcal strains^a

Drug and penicillin susceptibility ^b	MIC ($\mu\text{g/ml}$)		
	Range	MIC ₅₀	MIC ₉₀
Penicillin			
S	≤ 0.016 –0.06	≤ 0.016	0.03
I	0.125–1.0	1.0	1.0
R	2.0–4.0	2.0	4.0
Ertapenem			
S	≤ 0.008 –0.125	0.016	0.03
I	0.06–1.0	0.25	0.5
R	0.5–4.0	0.5	1.0
Amoxicillin			
S	≤ 0.016 –0.06	≤ 0.016	0.03
I	0.03–2.0	1.0	1.0
R	1.0–4.0	2.0	2.0
Cefprozil			
S	≤ 0.06 –16.0	0.125	0.25
I	0.25–16.0	4.0	8.0
R	8.0–32.0	16.0	16.0
Cefepime			
S	≤ 0.016 –0.25	≤ 0.016	0.06
I	0.125–2.0	1.0	1.0
R	1.0–4.0	1.0	2.0
Ceftriaxone			
S	≤ 0.016 –0.25	≤ 0.016	0.06
I	0.125–1.0	0.5	1.0
R	0.5–4.0	1.0	2.0
Imipenem			
S	≤ 0.008 –0.03	≤ 0.008	≤ 0.008
I	0.016–0.25	0.125	0.25
R	0.125–1.0	0.25	1.0
Meropenem			
S	≤ 0.008 –0.06	≤ 0.008	0.016
I	0.03–0.5	0.25	0.5
R	0.25–2.0	0.5	1.0
Clarithromycin			
S	≤ 0.03 –>32.0	≤ 0.03	>32.0
I	≤ 0.03 –>32.0	≤ 0.03	8.0
R	≤ 0.03 –>32.0	2.0	>32.0

^a Ciprofloxacin MIC, ≥ 4.0 $\mu\text{g/ml}$.^b S, susceptible; I, intermediate; R, resistant.

the MICs of all quinolones tested for all 64 strains for which ciprofloxacin MICs were ≥ 4 $\mu\text{g/ml}$ were increased, with the MICs at which 50% of isolates are inhibited (MIC₅₀s) and MIC₉₀s being as follows: ciprofloxacin, 32.0 and 64.0 $\mu\text{g/ml}$, respectively; levofloxacin, 16.0 and 32.0 $\mu\text{g/ml}$, respectively; sparfloxacin, 8.0 and 32.0 $\mu\text{g/ml}$, respectively; grepafloxacin, 4.0 and 16.0 $\mu\text{g/ml}$, respectively; gatifloxacin, 4.0 and 8.0 $\mu\text{g/ml}$, respectively; and moxifloxacin, 2.0 and 4.0 $\mu\text{g/ml}$, respectively. Ertapenem MIC₅₀s and MIC₉₀s were 0.016 and 0.03, 0.25 and 0.5, and 0.5 and 1.0 $\mu\text{g/ml}$ for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant strains for which quinolone MICs were increased, respectively. Moxifloxacin and gatifloxacin had the lowest MICs of all quinolones tested for strains for which ciprofloxacin MICs were ≥ 4.0 $\mu\text{g/ml}$.

Time-kill testing showed that after 12 h ertapenem at two

times the MIC was bacteriostatic (99% killing) against four penicillin-susceptible strains, four penicillin-intermediate strains, and four penicillin-resistant strains (Table 3) and after 24 h was bactericidal (99.9% killing) against all strains, with ertapenem at two times the MIC killing 90% of all strains after 6 h. After 24 h, ertapenem at the MIC was bacteriostatic against all strains tested. Regrowth was found after 24 h with ertapenem and meropenem at the MIC but not with imipenem at the MIC; this phenomenon was not found with the drugs at two times the MIC or higher.

When the killing kinetics were analyzed statistically, the bactericidal activity of imipenem at the MIC after 24 h was significantly greater ($P < 0.05$) than that of ertapenem. Conversely, the bactericidal activity of clarithromycin at all time periods and most MICs was lower than that of ertapenem ($P < 0.05$). The killing kinetics of all other compounds tested and at all other time periods and the MICs were similar to those of ertapenem.

DISCUSSION

Ertapenem is a new long-acting 1- β -methyl carbapenem antibiotic with potent activity which is comparable or superior to those of established agents against both gram-positive and -negative organisms in systemic and tissue infection models of disease. Ertapenem has a broad antibacterial spectrum and has activity against organisms which harbor extended-spectrum β -lactamases (7, 8, 16, 22). In a study of the activity of ertapenem against 545 gram-positive and gram-negative isolates, Fuchs and coworkers (7) found that ertapenem had greater activity against members of the family *Enterobacteriaceae* and poorer activity against *Pseudomonas aeruginosa* compared to that of imipenem. Advantageous pharmacokinetics, including an extended half-life and improved stability to renal dehydropeptidase I (8, 16, 22), support the development of this compound as an agent that can be used parenterally for the once-daily dosing of patients with serious infections.

Preliminary studies by Fuchs et al. (7) with a small number of strains have documented ertapenem MICs for penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci similar to those obtained in the present study. In our study, ertapenem MICs were similar to those of meropenem but, similar to previous findings, were 1 or 2 dilutions higher than those of imipenem (19). The ertapenem MICs for all strains tested were consistently 1 or 2 dilutions lower than those of broad-spectrum cephalosporins such as cefepime and ceftriaxone. The ertapenem MICs were similar to those of meropenem for all strains tested, irrespective of their macrolide or quinolone susceptibilities; and ertapenem at ≤ 4.0 $\mu\text{g/ml}$ inhibited all 285 strains tested and at ≤ 2.0 $\mu\text{g/ml}$, the proposed susceptibility breakpoint, inhibited 284 of 285 strains (99.7%) tested. Ertapenem also exhibited time-kill kinetics very similar to those of meropenem, with ertapenem at two times the MIC having bactericidal activity against all 12 strains tested after 24 h and significant killing at earlier time periods. The regrowth seen after 24 h with ertapenem and meropenem at the MIC but not with imipenem at the MIC may have been due, at least in part, to the instabilities of the carbapenems; however, fresh aliquots were used with each run. The killing kinetics of the three carbapenems at concentrations that were

TABLE 3. Results of tests of time-kill activities against 12 pneumococcal strains^a

Drug and multiple of the MIC	No. of strains for which there was the indicates changes in the no. of log ₁₀ CFU/ml ^b at the following times:											
	3 h			6 h			12 h			24 h		
	-1	-2	-3	-1	-2	-3	-1	-2	-3	-1	-2	-3
Ertapenem												
8	8	4	1	12	8	5	12	12	8	12	12	12
4	9	4	1	12	8	4	12	12	8	12	12	12
2	8	4	0	12	7	2	12	12	8	12	12	12
1	6	1	0	4	4	0	10	7	2	3	2	1
0.5	1	1	0	0	0	0	1	0	0	0	0	0
Amoxicillin												
8	9	3	0	11	8	5	12	12	9	12	12	12
4	10	2	0	11	8	2	12	12	8	12	12	12
2	7	2	0	9	7	1	12	10	7	12	12	12
1	4	0	0	7	3	0	10	7	3	10	10	9
0.5	1	0	0	2	1	0	0	0	0	0	0	0
Cefprozil												
8	10	2	0	11	5	2	12	11	6	12	12	11
4	9	1	0	11	6	2	12	11	7	11	11	11
2	7	1	0	9	3	1	12	11	6	11	11	11
1	6	1	0	8	4	0	10	7	2	7	7	5
0.5	3	0	0	0	0	0	0	0	0	0	0	0
Cefepime												
8	5	2	0	11	4	1	12	11	7	12	12	12
4	5	4	0	11	5	1	12	11	7	12	12	12
2	5	1	0	11	4	1	12	11	7	11	11	11
1	3	1	0	9	4	1	9	8	4	7	7	7
0.5	0	0	0	1	0	0	3	1	0	1	1	1
Ceftriaxone												
8	5	1	0	9	4	1	12	11	6	12	12	12
4	5	1	0	10	4	1	12	10	8	12	12	11
2	4	1	0	9	5	0	12	11	6	12	11	10
1	2	1	0	7	0	0	8	4	1	3	3	2
0.5	0	0	0	0	0	0	0	0	0	0	0	0
Imipenem												
8	9	3	0	12	10	2	12	12	9	12	12	12
4	10	4	0	12	9	0	12	12	9	12	12	12
2	10	1	0	12	8	2	12	11	8	12	12	10
1	8	1	0	9	6	1	11	10	5	11 ^c	11 ^c	7 ^e
0.5	1	0	0	2	0	0	0	0	0	0	0	0
Meropenem												
8	10	2	0	11	6	0 ^d	12	11	8	12	12	12
4	9	2	0	11	6	1	12	12	7	12	12	12
2	7	2	0	11	5	1	12	11	8	11	11	10
1	5	2	0	8	5	1	7	6	2	3	1	1
0.5 × MIC	0	0	0	1	0	0	1	0	0	0	0	0
Clarithromycin^e												
8	4	2	0	8	2 ^d	2	8	6 ^d	2 ^d	8	8	7 ^d
4	3 ^d	2	0	7 ^d	2 ^d	2	8	4 ^d	3	8	8	7 ^d
2	2 ^d	0	0	5 ^d	2	0	8	5 ^d	2 ^d	8	7 ^d	7 ^d
1	1 ^d	0	0	4	1	0	7	3	0	8	5	3
0.5	0	0	0	0	0	0	0	0	0	0	0	0

^a MICs were as follows: penicillin G, 0.016 to 4.0 µg/ml; ertapenem, 0.016 to 4.0 µg/ml; amoxicillin, 0.008 to 2.0 µg/ml; cefuroxime, 0.016 to 4.0 µg/ml; cefprozil, 0.03 to 4.0 µg/ml; cefepime, 0.016 to 4.0 µg/ml; ceftriaxone, 0.016 to 2.0 µg/ml; imipenem, 0.008 to 0.5 µg/ml; meropenem, 0.008 to 1.0 µg/ml; ciprofloxacin, 0.5 to 64.0 µg/ml (one strain was quinolone resistant); clarithromycin, 0.016 to >16.0 µg/ml (MICs were > 16.0 µg/ml for four strains).

^b Change in the number of log₁₀ CFU/ml compared to that at 0 h.

^c The bactericidal activity was significantly greater ($P < 0.05$) than that observed with ertapenem.

^d The bactericidal activity was significantly less ($P < 0.05$) than that observed with ertapenem.

^e Eight strains for which clarithromycin MICs were ≤0.03 µg/ml were tested.

two times the MIC and higher after 24 h were similar, but the significance of this difference is unknown. The activities of the other β-lactams tested were similar to those described previously (10–12, 18, 23), with the MICs of all compounds rising with those of penicillin.

The present study demonstrates that ertapenem has low MICs and very good killing kinetics, similar to those of meropenem, for all pneumococci, irrespective of their macrolide or quinolone susceptibility status. In addition to the known problem of macrolide resistance (12), strains for which quinolone MICs are increased have recently been described from Hong Kong and Canada (3, 9), and these strains may become more widespread. Clinical studies are necessary in order to validate the in vitro and pharmacokinetic properties of ertapenem.

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