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In Vitro Activity of *N*-Formimidoyl Thienamycin (MK0787)

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The in vitro activity of *N*-formimidoyl thienamycin (MK0787), a stable congener of thienamycin, was determined against 200 species of aerobic and 84 species of anaerobic bacteria. The compound was highly active against resistant gram-negative bacilli, penicillin-resistant *Staphylococcus aureus*, enterococci, and anaerobic bacteria. The new derivative of thienamycin was more active than the parent compound, probably reflecting the stability of the analog.

N-Formimidoyl thienamycin (MK0787) is a stable crystalline derivative of thienamycin (4). Previous studies from this laboratory have demonstrated that thienamycin has broad antimicrobial activity against both aerobic and anaerobic bacteria (5). For example, thienamycin was highly active against gram-negative bacilli and penicillin-resistant *Staphylococcus aureus*. In addition, the activity of this novel β-lactam antibiotic against anaerobic bacteria was comparable to that of metronidazole. However, the parent compound, lacking stability at high concentrations, was considered unsuitable as a therapeutic agent for serious infections. MK0787 is a congener of thienamycin that appears to possess the stability and antimicrobial spectrum of a clinically useful drug. This report documents the excellent in vitro activity of MK0787 against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria.

Standard antibiotic powders were obtained from the following sources: thienamycin and cefoxitin from Merck Institute of Research, Rahway, N.J.; carbenicillin from Roerig Laboratories, New York, N.Y.; penicillin G, ampicillin, and amikacin from Bristol Laboratories, Syracuse, N.Y.; nafcillin from Wyeth Laboratories, Philadelphia, Pa.; cefamandole from Eli Lilly Laboratories, Indianapolis, Ind.; clindamycin from The Upjohn Co., Kalamazoo, Mich.; chloramphenicol from Sigma Chemical Co., St. Louis, Mo.; and metronidazole from G. D. Searle & Co., Chicago, Ill. All antibiotic solutions were prepared fresh on the day used. Thienamycin was solubilized in distilled water. The aqueous solution was filtered and sterilized before use. The following ranges of concentrations of antimicrobial agents (in micrograms per milliliter) were used: thienamycin, 8 to 0.125; gentamicin, amikacin, ampicillin, and nafcillin, 64 to 0.125; clindamycin and metronidazole, 32 to 0.125; and carbenicillin, penicillin, cefamandole, and cefoxitin, 256 to 0.125. The facultative aerobic bacteria were isolated at the Tufts-New England Medical Center clinical bacteriology laboratory. Identification of the isolates was carried out by using the criteria of Blair et al. (2). The anaerobic bacteria were isolated from clinical specimens processed at the Tufts Anaerobic Research Laboratory and identified by previously described techniques (3). One strain of *Bacteroides fragilis* highly resistant to clindamycin was laboratory derived; the metronidazole-resistant isolate was obtained from H. Ingram, Newcastle, England. Control organisms included *Escherichia coli* ATCC 25992, *S. aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *B. fragilis* TAL 10, and *Peptococcus magnus* TAL 169. The control anaerobic strains were originally obtained from Vera Sutter (Los Angeles, Calif.) and have been used routinely as control strains in our laboratory. Antibiotic susceptibility of aerobes and facultative organisms was determined by the microtiter technique; the susceptibility of anaerobes was determined by a modification of the agar dilution method. Both procedures have been described previously (1, 5).

MK0787 possessed excellent activity against all of the gram-negative facultative bacilli tested, including *E. coli* and *P. aeruginosa* (Table 1). All tested bacteria in this group were inhibited by 4 μg or less/ml, except one strain of *Serratia* that required 8 μg/ml for inhibition. MK0787 was more active than gentamicin, amikacin, or carbenicillin against gram-negative bacilli and was even active against organisms resistant to these three compounds.

This new analog of thienamycin possessed good activity against most facultative gram-positive cocci (Table 1). It had activity similar to that of nafcillin against *S. aureus*. MK0787 also displayed good activity against enterococci. The only notable exception was *Staphylococcus epidermidis*, 3 of 20 strains of which were resistant, requiring 32 μg/ml for inhibition.

MK0787 showed excellent activity against the anaerobic bacteria tested (Table 1). All isolates

TABLE 1. *Comparative activities of antibiotics against facultative and anaerobic bacteria*

Bacteria	No. of strains	Antibiotic	Minimal inhibitory conc (μg/ml)		
			Active against:		Range
			50%	90%	
E. coli	21	Thienamycin	≤0.125	0.5	≤0.125–0.5
		Gentamicin	0.5	1	0.5–16
		Amikacin	1	16	1–32
		Carbenicillin	4	>256	1–>256
Klebsiella	20	Thienamycin	0.5	0.5	≤0.125–1
		Gentamicin	1	>64	0.5–>64
		Amikacin	2	4	1–8
		Carbenicillin	>256	>256	16–>256
Enterobacter	20	Thienamycin	0.5	2	0.5–2
		Gentamicin	0.5	4	0.5–8
		Amikacin	2	4	1–16
		Carbenicillin	4	8	1–64
Serratia	20	Thienamycin	1	2	0.5–8
		Gentamicin	2	32	0.5–64
		Amikacin	4	16	2–32
		Carbenicillin	16	>256	2–>256
Proteus (indole positive)	12	Thienamycin	2	2	0.5–4
		Gentamicin	0.5	0.5	≤0.125–0.5
		Amikacin	1	2	0.5–2
		Carbenicillin	4	4	0.5–>256
Salmonella and Citrobacter	10	Thienamycin	0.5	0.5	≤0.125–0.5
		Gentamicin	0.5	0.5	0.5–1
		Amikacin	2	4	1–4
		Carbenicillin	4	64	1–64
Pseudomonas aeruginosa	21	Thienamycin	4	4	1–4
		Gentamicin	4	8	4–16
		Amikacin	4	16	2–16
		Carbenicillin	32	64	16–128
Haemophilus influenzae	9	Thienamycin	0.5	1.0	0.5–1
		Ampicillin	4.0	4.0	1–4
		Chloramphenicol	4.0	4.0	2–4
		Cefamandole	4.0	8.0	1–8
		Cefoxitin	8.0	8.0	4–8
Streptococci	9	Thienamycin	≤0.125	2	≤0.125–2
		Penicillin	≤0.125	0.5	≤0.125–0.5
		Nafcillin	0.5	1	≤0.125–1
Enterococci	13	Thienamycin	2	2	1–8
		Penicillin	4	8	4–16
		Nafcillin	4	64	4–64
S. aureus	25	Thienamycin	≤0.125	≤0.125	≤0.125–0.5
		Penicillin	2	16	≤0.125–64
		Nafcillin	0.25	0.5	≤0.125–1
S. epidermidis	20	Thienamycin	1	32	≤0.125–32
		Penicillin	4	64	≤0.125–>256
		Nafcillin	0.5	8	≤0.125–64

TABLE 1—*Continued*

Bacteria	No. of strains	Antibiotic	Minimal inhibitory conc (μg/ml)		
			Active against:		Range
			50%	90%	
B. fragilis	56	Thienamycin	0.5	1	≤0.125–1
		Penicillin	16	>256	0.5–>256
		Cefoxitin	4	16	1–64
		Clindamycin	≤0.125	1	≤0.125–>256
		Metronidazole	0.5	1	0.5–16
Anaerobic gram-positive cocci	14	Thienamycin	0.5	2	≤0.125–2
		Penicillin	≤0.125	0.5	≤0.125–1
		Cefoxitin	0.5	8	0.5–8
		Clindamycin	0.5	4	≤0.125–32
		Metronidazole	0.5	2	≤0.125–32
Clostridia	14	Thienamycin	≤0.125	0.5	≤0.125–0.5
		Penicillin	≤0.125	1	≤0.125–16
		Cefoxitin	2	4	≤0.125–4
		Clindamycin	≤0.125	0.5	≤0.125–0.5
		Metronidazole	0.5	1	≤0.125–1

of *B. fragilis* were susceptible, including eight strains highly resistant to penicillin. The activity of this new agent against anaerobic bacteria was greater than those of clindamycin, cefoxitin, and metronidazole and was distinctly better than that of penicillin G. The activity of MK0787 was similar to those of penicillin G, clindamycin, and metronidazole against anaerobic gram-positive cocci and clostridia and was superior to that of cefoxitin. All anaerobic organisms were inhibited by 2 μg or less of MK0787 per ml, whereas certain of these organisms required 16 to 32 μg of the other agents per ml for inhibition.

The results of the study indicate that MK0787 is more active against a broad range of bacteria than is its parent compound, thienamycin. This improved activity probably reflects the stability of the new analog (4). MK0787 was the most active antimicrobial agent tested against gram-negative facultative bacilli, demonstrating superior results compared with gentamicin, amikacin, and carbenicillin; the only exception was somewhat increased activity of gentamicin against some indole-positive strains of *Proteus*. In comparing this new compound with other β-lactam antibiotics, its activity is superior to those of moxalactam and cefotaxime, especially against strains of *Enterobacter*, *Proteus*, *Serratia*, *Pseudomonas*, and *S. aureus* (1). The activity of MK0787 against *E. coli* and *Klebsiella* sp. was similar to those of moxalactam and cefotaxime (1).

MK0787 possessed potent antimicrobial activity against a variety of anaerobic pathogens. Its activity against *B. fragilis* was greater than those of clindamycin and metronidazole; indeed, none of the tested strains of *B. fragilis* required more than 1.0 μg of MK0787 per ml for inhibition. This drug also inhibited *B. fragilis* strains that were highly resistant to other antibiotics, including strains known to produce high levels of β-lactamase, those with high resistance to clindamycin, and the only strain resistant to metronidazole so far isolated. The uniform activity of MK0787 against *B. fragilis* at low concentrations indicates that it effectively penetrates to the active site and is most likely resistant to the β-lactamases (6).

MK0787 also displayed good activity against anaerobic gram-positive cocci and clostridia.

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