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Activity of *N*-Formimidoyl Thienamycin and Cephalosporins Against Isolates from Nosocomially Acquired Bacteremia

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The in vitro activity of *N*-formimidoyl thienamycin was compared with that of seven beta-lactam agents against bacteremic clinical isolates, including gentamicin-resistant, gram-negative bacilli, *Staphylococcus aureus*, *Staphylococcus epidermidis*, streptococci, and enterococci. *N*-formimidoyl thienamycin was the most active antibiotic against all of the gram-positive cocci studied, with the exception of *Staphylococcus epidermidis*, and the only agent active against the enterococci. *N*-formimidoyl thienamycin was less active than some of the other agents against *Enterobacteriaceae*, except for the strains of *Serratia* and *Citrobacter* studied. For *Pseudomonas aeruginosa*, *N*-formimidoyl thienamycin was the most active agent (4 μg/ml was the lowest concentration that inhibited 90% of the strains tested).

Infection continues to be a major cause of morbidity and mortality in hospitalized patients. The search for new broad-spectrum drugs with low toxicity continues to be important. Thienamycin (1, 4) is a new beta-lactam antibiotic which has exhibited potent, broad-spectrum activity against a wide variety of organisms, including isolates exhibiting resistance to several currently available antibiotics (3, 5, 8, 9, 11).

This study investigates the activity of this new compound against a variety of nosocomial bacterial strains and compares it with seven beta-lactam agents: cephalothin, cefamandole, cefoxitin, moxalactam, cefotaxime, cefoperazone, and ceftizoxime.

N-formimidoyl thienamycin and cefoxitin were supplied by the Merck Institute for Therapeutic Research (Rahway, N.J.); cephalothin, cefamandole, and moxalactam were supplied by Eli Lilly & Co. (Indianapolis, Ind.); cefotaxime was supplied by Hoechst-Roussel Pharmaceuticals (Somerville, N.J.); cefoperazone was supplied by Pfizer Inc. (New York, N.Y.); and ceftizoxime was supplied by Smith Kline & French Laboratories (Philadelphia, Pa.). Laboratory standard powders were diluted as recommended by the manufacturers to stock concentrations of 1,000 μg/ml and used immediately or frozen at −80°C for up to 2 weeks until used.

The organisms studied included 300 bacterial strains isolated from blood cultures of hospitalized patients at the Puerto Rico Medical Center and Veterans Administration Hospital, recovered between January 1979 and June 1980, lyophilized, and reconstituted fresh to determine susceptibility patterns. The isolates included 100 strains of gram-positive cocci (see Table 1) and 200 strains of gram-negative bacilli, including 96 strains of gentamicin-resistant, gram-negative bacilli (see Table 2). The identity of all isolates was confirmed by standard microbiological methods (6). The enterococcal strains included 11 strains of *Streptococcus faecalis*, 7 of *Streptococcus faecalis* subsp. *liquefaciens*, 4 of *Streptococcus faecalis* subsp. *zymogenes*, 2 of *Streptococcus durans*, and 1 of *Streptococcus faecium*. The streptococcal strains included 15 strains of group B streptococci, 4 of *S. viridans*, 3 of *S. sanguis*, 2 of *S. mutans*, and 1 strain of group A streptococci. The *Serratia* strains studied included 18 of *S. liquefaciens* and 7 of *S. marcescens*. The *Citrobacter* strains included 18 of *C. diversus* and 7 of *C. freundii*. There were 12 *Proteus mirabilis* and 13 strains of indole-positive proteus, including 8 *Morganella morganii* and 5 *Proteus vulgaris*.

Minimal inhibitory concentrations (MICs) of the antibiotics were determined simultaneously and in duplicate for each bacterial strain by standard microdilution methods with the Dynatech MIC-2000 System (Dynatech Laboratories, Alexandria, Va.) (2, 7). For all of the organisms, with the exception of the enterococci, the antibiotics were diluted in Mueller-Hinton broth. For the enterococci, brain heart infusion broth was used.

The lowest concentration of antibiotic which inhibited all usually apparent growth was considered the MIC. Control strains *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa*

ATCC 27853, and *Staphylococcus aureus* ATCC 25923 were included in each group tested. For each antibiotic-organism combination, MIC_{50} was the lowest concentration of antibiotic which inhibited at least 50% of the strains tested, and MIC_{90} was the lowest concentration which inhibited at least 90% of the strains tested. The minimum bactericidal concentration was determined for all strains.

The comparative in vitro activity of the eight antibiotics against staphylococci and streptococci is shown in Table 1. *N*-formimidoyl thienamycin was the most active antibiotic against *Staphylococcus aureus* and the streptococci, including the enterococci. Cephalothin was the most active agent against *Staphylococcus epidermidis*. Cefoxitin and moxalactam were the least active of the drugs against gram-positive cocci. Concentrations of ≤0.0625, 2, and 0.125 μg of *N*-formimidoyl thienamycin per ml inhibited 90% of the strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and streptococci, respectively. *N*-formimidoyl thienamycin was the only beta-lactam antibiotic studied with effectiveness against enterococci, inhibiting 100% of the strains at a concentration of ≤2 μg/ml.

The comparative in vitro activities of the eight antibiotics against *Enterobacteriaceae* and *Pseudomonas aeruginosa* are shown in Table 2. Moxalactam, cefotaxime, and ceftizoxime were the most active drugs against all of the *Enterobacteriaceae*. *Serratia* and *Citrobacter* strains were equally susceptible to *N*-formimidoyl thienamycin. There were no differences in the susceptibilities of the different strains of gram-negative bacilli to *N*-formimidoyl thienamycin.

N-formimidoyl thienamycin was the most active agent against *Pseudomonas aeruginosa*, and cefotaxime and cefoperazone were intermediate in activity. Concentrations of 4 μg of *N*-formimidoyl thienamycin per ml and 16 μg or less of cefotaxime and cefoperazone per ml

TABLE 1. Comparative in vitro activity of *N*-formimidoyl thienamycin, cephalothin, cefamandole, cefoxitin, moxalactam, cefotaxime, cefoperazone, and ceftizoxime against staphylococci and streptococci

Organism (no. of strains)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Staphylococcus aureus (25)	*N*-formimidoyl thienamycin	≦0.0625	≦0.0625	≦0.0625
	Cephalothin	0.25–1.0	0.5	0.5
	Cefamandole	0.25–2.0	1.0	2.0
	Cefoxitin	2–8	4	4
	Moxalactam	4–16	8	8
	Cefotaxime	≦0.0625–2	0.25	2
	Cefoperazone	2–4	4	4
	Ceftizoxime	2–16	4	8
Staphylococcus epidermidis (25)	*N*-formimidoyl thienamycin	≦0.0625–4	1	2
	Cephalothin	0.125–1	0.25	0.5
	Cefamandole	0.25–2	0.5	1
	Cefoxitin	1–8	2	8
	Moxalactam	8–64	8	32
	Cefotaxime	≦0.0625–2	≦0.0625	1
	Cefoperazone	1–4	2	4
	Ceftizoxime	0.25–32	0.5	16
Streptococcus spp. (25)	*N*-formimidoyl thienamycin	≦0.0625–0.125	≦0.0625	0.125
	Cephalothin	≦0.0625–4	0.125	0.5
	Cefamandole	≦0.0625–4	0.125	0.5
	Cefoxitin	0.5–64	4	4
	Moxalactam	0.5–32	4	16
	Cefotaxime	≦0.0625–1	≦0.0625	0.25
	Cefoperazone	≦0.0625–1	0.125	1
	Ceftizoxime	≦0.0625–0.25	≦0.0625	0.25
Enterococci (25)	*N*-formimidoyl thienamycin	0.5–2	1	2
	Cephalothin	16–32	32	32
	Cefamandole	16–64	32	32
	Cefoxitin	>128	>128	>128
	Moxalactam	>128	>128	>128
	Cefotaxime	1–>128	2	128
	Cefoperazone	16–64	32	64
	Ceftizoxime	64–>128	>128	>128

TABLE 2. Comparative in vitro activity of *N*-formimidoyl thienamycin, cephalothin, cefamandole, cefoxitin, moxalactam, cefotaxime, cefoperazone, and ceftizoxime against *Enterobacteriaceae* and *Pseudomonas aeruginosa*

Organism (no. of strains)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Escherichia coli (25)	*N*-formimidoyl thienamycin	0.25–0.5	0.25	0.5
	Cephalothin	0.25–64	8	32
	Cefamandole	0.25–32	1	16
	Cefoxitin	0.5–8	2	4
	Moxalactam	≦0.0625–0.5	0.25	0.25
	Cefotaxime	≦0.0625	≦0.0625	≦0.0625
	Cefoperazone	≦0.0625–8	0.125	4
	Ceftizoxime	≦0.0625	≦0.0625	≦0.0625
Klebsiella pneumoniae (25)	*N*-formimidoyl thienamycin	0.25–0.5	0.5	0.5
	Cephalothin	1–>128	8	64
	Cefamandole	0.25–>128	2	64
	Cefoxitin	0.5–128	0.5	4
	Moxalactam	≦0.0625–4	0.125	0.5
	Cefotaxime	≦0.0625–0.125	≦0.0625	≦0.0625
	Cefoperazone	≦0.0625–16	1	1
	Ceftizoxime	≦0.0625–0.25	≦0.0625	≦0.0625
Enterobacter cloacae (25)	*N*-formimidoyl thienamycin	≦0.5–2	0.5	2
	Cephalothin	4–>128	>128	>128
	Cefamandole	0.5–>128	16	>128
	Cefoxitin	4–>128	128	>128
	Moxalactam	≦0.0625–1.0	0.125	0.5
	Cefotaxime	≦0.0625–2.0	≦0.0625	0.5
	Cefoperazone	≦0.0625–16	1	8
	Ceftizoxime	≦0.0625–2	≦0.0625	0.5
Serratia (25)	*N*-formimidoyl thienamycin	0.25–1	0.5	1
	Cephalothin	>128	>128	>128
	Cefamandole	16–>128	64	>128
	Cefoxitin	0.5–64	16	64
	Moxalactam	0.25–2	0.25	0.5
	Cefotaxime	≦0.0625–1	0.125	0.5
	Cefoperazone	1–128	8	16
	Ceftizoxime	≦0.0625–2	0.25	1.0
Citrobacter (25)	*N*-formimidoyl thienamycin	0.25–0.5	0.5	0.5
	Cephalothin	4–>128	16	>128
	Cefamandole	0.5–128	2	64
	Cefoxitin	0.5–128	4	32
	Moxalactam	≦0.0625–0.5	0.125	0.5
	Cefotaxime	≦0.0625–2	0.125	0.5
	Cefoperazone	≦0.0625–32	2	16
	Ceftizoxime	≦0.0625–0.5	≦0.0625	0.25
Proteus (25)	*N*-formimidoyl thienamycin	2–4	2	4
	Cephalothin	2–>128	8	>128
	Cefamandole	0.25–>128	1	16
	Cefoxitin	1–>128	4	8
	Moxalactam	≦0.0625–0.5	0.25	0.25
	Cefotaxime	≦0.0625–0.125	≦0.0625	≦0.0625
	Cefoperazone	0.25–16	0.5	4
	Ceftizoxime	≦0.0625–16	≦0.0625	0.5
Providencia stuartii (25)	*N*-formimidoyl thienamycin	1–4	2	4
	Cephalothin	128–>128	>128	>128
	Cefamandole	0.5–64	4	16
	Cefoxitin	1–64	4	16
	Moxalactam	≦0.0625–0.5	0.125	0.5
	Cefotaxime	≦0.0625–8	≦0.0625	0.25

TABLE 2—*Continued*

Organism (no. of strains)	Antibiotic	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	Cefoperazone	0.5–16	2	4
	Ceftizoxime	≦0.0625–32	≦0.0625	≦0.0625
Pseudomonas aeruginosa (25)	*N*-formimidoyl thienamycin	0.5–4	2	4
	Cephalothin	>128–>128	>128	>128
	Cefamandole	>128–>128	>128	>128
	Cefoxitin	>128–>128	>128	>128
	Moxalactam	4–32	16	32
	Cefotaxime	2–16	8	16
	Cefoperazone	2–32	4	16
	Ceftizoxime	4–64	32	64

inhibited 90% of the *Pseudomonas aeruginosa* strains tested. Gentamicin-susceptible and gentamicin-resistant strains were equally susceptible to *N*-formimidoyl thienamycin.

N-formimidoyl thienamycin activity is greater than that of first-, second-, and third-generation cephalosporins against *Staphylococcus aureus*, streptococci, and enterococci. *N*-formimidoyl thienamycin is less active than cephalothin against *Staphylococcus epidermidis*. A concentration of 0.5 μg of cephalothin per ml inhibited 90% of the *Staphylococcus epidermidis* strains tested; a concentration of 2 μg of *N*-formimidoyl thienamycin per ml was required to inhibit 90% of the strains. A concentration of 2 μg of *N*-formimidoyl thienamycin per ml inhibited 100% of the strains of enterococci tested; *N*-formimidoyl thienamycin was the only beta-lactam antibiotic studied with significant activity against these microorganisms.

Moxalactam, cefotaxime, and ceftizoxime were the most active drugs against the organisms of the *Enterobacteriaceae* group, including gentamicin-resistant strains. *Serratia* and *Citrobacter* strains were equally susceptible to *N*-formimidoyl thienamycin. *N*-formimidoyl thienamycin was the most active agent against *Pseudomonas aeruginosa*, and cefotaxime and cefoperazone were of intermediate activity. These results are similar to recent reports on the in vitro activity of *N*-formimidoyl thienamycin, moxalactam, cefotaxime, ceftizoxime, and cefoperazone (10).

Because of its remarkable activity against many clinically encountered pathogens, including *Pseudomonas aeruginosa* and enterococci, *N*-formimidoyl thienamycin appears to be an especially promising drug. Further studies of its pharmacokinetics, in vivo activity, and toxicity will be of interest.

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