ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1980, p. 750-756
0066-4804/80/04-0750/07$02.00/0

Vol. 17, No. 4

Moxalactam (LY127935), a New Semisynthetic 1-Oxa-β-Lactam Antibiotic with Remarkable Antimicrobial Activity: In Vitro Comparison with Cefamandole and Tobramycin

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Moxalactam (LY127935) exhibited greater in vitro activity than cefamandole and tobramycin against clinical isolates of *Enterobacteriaceae*, *Aeromonas hydrophila*, and *Pseudomonas maltophilia*. The activities of the three drugs against other microorganisms were as follows: for staphylococci, cefamandole = tobramycin > moxalactam; for streptococci, cefamandole > moxalactam > tobramycin; and for *Pseudomonas aeruginosa*, tobramycin > moxalactam > cefamandole. Moxalactam also demonstrated significant activity against the *Bacteroides fragilis* group and other anaerobes. Moxalactam was comparable to cefotaxime (HR756) in its inhibition of cephalothin-resistant and aminoglycoside-resistant clinical isolates.

Organisms in numerous genera and species have developed antimicrobial resistance to commonly used compounds such as the beta-lactams. Pharmaceutical research has responded to this microbial challenge by the modification of various antimicrobial agents, thus rendering them refractory to inactivating bacterial enzymes while significantly increasing antimicrobial activity and spectrum (1, 3, 7, 8, 10-12, 16). Moxalactam (LY127935) (Lilly), also designated 6059-S (Shionogi), is a novel 1-oxa-β-lactam antibiotic having the chemical name (6R,7R)-7-{[carboxy (4-hydroxyphenyl) acetyl] amino}-7-methoxy-3-{[(1-methyl-1H-tetrazol-5-yl)thio} methyl]-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, disodium. This antibiotic is structurally similar to cefamandole, yet differs in the 4-hydroxy of the phenyl ring, a 7-methoxy group, and the substitution of an oxygen for the 1-sulfa in the cephem ring. Moxalactam is reported to have a broad spectrum and a highly potent antimicrobial activity against *Pseudomonas aeruginosa*, enterobacters, indole-positive *Proteus* species, *Serratia marcescens*, and *Bacteroides fragilis* group (2, 6, 15, 18-20).

In this collaborative six-medical center in vitro evaluation, we principally compared the antimicrobial activity of moxalactam with those of a broad-spectrum cephalosporin (cefamandole) and an aminoglycoside (tobramycin).

The study compound moxalactam and reference antimicrobial agents (cefamandole and tobramycin) were received as a gift from Eli Lilly and Co., Indianapolis, Ind. Moxalactam was an equal mixture of D and L isomers (lot SI-113-8B).

The bacterial strains studied were those consecutive clinical strains isolated during a 45- to 60-day interval at the six participating laboratories. The number of isolates tested was 8,371, including 4,679 *Enterobacteriaceae*, 860 nonenteric gram-negative bacilli, 851 streptococci, 1,531 staphylococci, and 150 selected antibiotic-resistant strains. All organisms were identified and processed by methods previously described (7, 8, 11, 12). In addition, 248 anaerobic organisms were tested by broth microdilution and agar dilution methods (9, 13) after identification by gas-liquid chromatography and biochemical micro-tube procedures (9).

The minimum inhibitory concentrations (MICs) of all study compounds were determined by agar dilution methods or microdilution broth procedures. In the broth microdilution procedure, Mueller-Hinton broth (Difco) was supplemented with 50 mg of calcium and 25 mg of magnesium per liter. Media and antibiotics were dispensed into plastic trays utilizing the MIC-2000 (Cooke Laboratory Products, Alexandria, Va.) by techniques previously reported (7, 8, 11, 12). Agar dilution tests were performed after the method of the International Collaborative Study (4) using Mueller-Hinton agar inoculated by a Steers replicator (17) with an inoculum density

of ca. 10^4 colony-forming units per spot. The antibiotic-containing agar plates and microdilution trays were incubated for 15 to 18 h at 35°C. The effect of inoculum concentrations of 10^3, 10^5, and 10^7 colony-forming units per ml on the MICs was also determined.

Intra- and interlaboratory MIC variations were assessed using four quality control strains

TABLE 1. *In vitro antimicrobial activity comparison of moxalactam, tobramycin, and cefamandole against 4,679 recent clinical isolates of Enterobacteriaceae*

Organism (no.)	Antibiotic	Cumulative %[a] of isolates inhibited at MIC (μg/ml) of:						
		<0.5	1	2	4	8	16	32
Citrobacter diversus (36)	Moxalactam	**97**	100					
	Tobramycin	**83**	97	100				
	Cefamandole	**50**	78	86	94	97		
C. freundii (110)	Moxalactam	**82**	86	88	95	98	99	100
	Tobramycin	**64**	94	96				
	Cefamandole	**53**	69	73		74	77	78
Enterobacter aerogenes (160)	Moxalactam	**77**	79	85	92	94	97	99
	Tobramycin	**57**	86	88		92	97	99
	Cefamandole	28	**52**	61	71	78	80	81
E. agglomerans (26)	Moxalactam	**77**	81		88	92	96	
	Tobramycin	**81**	85	100				
	Cefamandole	31	**65**	81	85			88
E. cloacae (201)	Moxalactam	**79**	86	86	88	91	93	98
	Tobramycin	**66**	95	97	97	98	98	99
	Cefamandole	15	35	**60**	74	78	81	82
Escherichia coli (2572)	Moxalactam	**93**	97	97	98	99	99	99
	Tobramycin	41	**85**	93	96	98	99	99
	Cefamandole	**63**	82	88	92	96	97	98
Klebsiella oxytoca (101)	Moxalactam	**92**	97	98	99	100		
	Tobramycin	**66**	99	100				
	Cefamandole	**45**	73	88	91	92	94	97
K. pneumoniae (570)	Moxalactam	**93**	96	97	97	98	99	
	Tobramycin	**70**	95	97	97	98	99	99
	Cefamandole	**48**	77	83	89	94	95	96
Morganella morganii (103)	Moxalactam	**88**	92	93	96		97	
	Tobramycin	**51**	74	82	94	97	98	
	Cefamandole	5	18	28	31	40	**62**	76
Proteus mirabilis (424)	Moxalactam	**94**	97	98	98	99	99	99
	Tobramycin	**54**	89	99	99	99	100	
	Cefamandole	**48**	85	95	97	97	97	98
P. vulgaris (30)	Moxalactam	**90**				97	100	
	Tobramycin	**60**	87	93	97	100		
	Cefamandole	3	7	10		17	23	33
Providencia rettgeri (13)	Moxalactam	**100**						
	Tobramycin	**46**	85	100				
	Cefamandole	**69**		77	92	100		
P. stuartii (30)	Moxalactam	**93**	97	100				
	Tobramycin	7	13	37	**63**	80	90	93
	Cefamandole	**53**	67	90	97			
Salmonella enteritidis (18)	Moxalactam	**100**						
	Tobramycin		22	**100**				
	Cefamandole	**72**	100					
Serratia marcescens (227)	Moxalactam	**52**	66	84	88	93	96	99
	Tobramycin	5	26	**55**	66	72	74	75
	Cefamandole	2			3	10	18	30
Other *Enterobacteriaceae* species (58)[b]	Moxalactam	**91**	93	97			98	
	Tobramycin	64	86	98				
	Cefamandole	**29**	50	58	67	75	81	85

[a] Boldfaced numbers represent the mode if within or below the dilution range tested.

[b] Includes (number of strains): *Arizona arizona* (2), *Citrobacter amalonatica* (6), *E. coli* AD group (12), *Hafnia alvei* (13), *Klebsiella ozaenae* (6), *Providencia alcalifaciens* (2), *Salmonella typhi* (2), *Serratia liquifaciens* (6), and *Shigella* species (9).

with known reproducible MICs. The organisms included *Escherichia coli* (ATCC 25922 or K380), *P. aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923 or 29213), and *Streptococcus faecalis* (ATCC 29212). Approximately 98% of all tabulated MICs (462 total) were within 1 $\log_2$ dilution interval from the mode. Statistical analysis of laboratory, media, and antimicrobial activity differences was calculated using the Kalmozorov-Smironov test (8).

Moxalactam demonstrates remarkable activity against all the *Enterobacteriaceae* (Table 1). The moxalactam modal MIC was ≤0.5 μg/ml for all species, compared to the range of ≤0.5 to >32 μg/ml for cefamandole and ≤0.5 to 4 μg/ml for tobramycin. The increased in vitro activity of moxalactam over both cefamandole and tobramycin statistically significant ($P = < 0.001$) for *Enterobacter cloacae, E. coli, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis,* and *S. marcescens.* Lesser degrees of significance ($P = < 0.05$ or $P = < 0.01$) were found favoring moxalactam against *Enterobacter agglomerans* and *Providencia stuartii* compared to cefamandole, and moxalactam against *Enterobacter aerogenes* and *Klebsiella oxytoca* when

TABLE 2. *Modal MIC and those MICs inhibiting 75 and 90% of 3,294 isolates of gram-positive cocci and non-Enterobacteriaceae gram-negative bacilli*

Organism (no.)	Moxalactam MIC (μg/ml)			Tobramycin MIC (μg/ml)			Cefamandole MIC (μg/ml)		
	Mode	MIC_{75}[a]	MIC_{90}[a]	Mode	MIC_{75}	MIC_{90}	Mode	MIC_{75}	MIC_{90}
Staphylococcus aureus (936)	8	8	16	≤0.5	≤0.5	4	≤0.5	≤0.5	1
S. epidermidis (583)	8	16	>32	≤0.5	8	32	≤0.5	1	2
Streptococcus faecalis (680)	>32	>32	>32	32	32	>32	32	32	>32
Streptococcus group D not *faecalis* (34)	>32	>32	>32	>32	>32	>32	>32	>32	>32
S. agalactiae (49)	8	8	16	16	>32	>32	≤0.5	≤0.5	≤0.5
S. pyogenes (17)	1, 2	2	4	32	32	32	≤0.5	≤0.5	≤0.5
Beta-streptococci, not group A, B, or D (17)	2	16	32	32	32	32	≤0.5	≤0.5	1
S. pneumoniae (23)	2	2	2	16	16	32	≤0.5	≤0.5	≤0.5
Viridans group (31)	≤0.5	8	16	≤0.5	16	32	≤0.5	1	8
Other gram-positive bacteria[b] (64)	≤0.5	16	>32	≤0.5	2	8	≤0.5	8	32
Aeromonas hydrophila (13)	≤0.5	≤0.5	16	≤0.5, 4	4	4	≤0.5	2	>32
Acinetobacter calcoaceticus subsp. *anitratus* (76)	>32	>32	>32	≤0.5	2	4	>32	>32	>32
A. calcoaceticus subsp. *lwoffi* (24)	8	16	32	≤0.5	32	>32	32, >32	32	>32
Moraxella sp. (17)	≤0.5	≤0.5	2	≤0.5	≤0.5	2	≤.05	2	8
Pseudomonas aeruginosa (638)	16	32	>32	1	2	4	>32	>32	>32
P. maltophilia (37)	4	16	>32	>32	>32	>32	>32	>32	>32
Pseudomonas spp.[c] (36)	16	32	>32	≤0.5	1	8	>32	>32	>32
Other nonenteric gram-negative bacilli[d] (19)	4	4	16	>32	>32	>32	≤0.5, 16	16	>32

[a] MIC_{75}, MIC_{90}, MICs inhibiting 75 and 90%, respectively, of isolates tested.

[b] Includes (number of isolates): various nonhemolytic ungroupable streptococci (23), *Bacillus* spp. (13), *Corynebacterium* spp. (13), *L. monocytogenes* (3), and *Micrococcus* spp. (12).

[c] Includes *Pseudomonas* sp. NOS (31), *P. fluorescens* (2), and *P. putida* (3).

[d] Includes *Achromobacter xylosoxidans* (9), *Alcaligenes* spp. (2), *Flavobacterium* spp. (2), CDC group IVc (1), and *Pasteurella multocida* (5).

compared to tobramycin. A comparison of agar and broth dilution MICs by enteric species showed no significant ($P = > 0.05$) difference in moxalactam MIC results. In contrast, cefamandole broth MICs were consistently and significantly higher for *Citrobacter freundii*, *E. cloacae*, *E. aerogenes*, and *M. morganii* (5). The opposite phenomenon was found for *E. coli*, *K. pneumoniae*, and *P. mirabilis*. Only one significant moxalactam media MIC difference involving the "other gram-negative bacteria" was noted; it favored higher moxalactam activity against *P. aeruginosa* when tested by the agar dilution procedures.

The anti-staphylococcal activity of moxalactam was markedly less than that of cefamandole or tobramycin (Table 2). Cephalothin had approximately 16-fold-lower staphylococcal MICs. However, 97.4% of the 936 *S. aureus* isolates were inhibited by ≤32 μg of moxalactam per ml, which is said to be a readily achievable serum concentration (R. Kammer, personal communication). This compares to 96.0 and 98.1% inhibition at concentrations of 1 and 8 μg of cefamandole per ml. Significantly higher *S. aureus* ($P = < 0.001$) moxalactam broth MICs were found, though moxalactam broth and agar modal MICs were identical. Similar activity and media results were encountered for the *Streptococcus epidermidis* isolates tested. The activ-

TABLE 3. *Comparative in vitro antimicrobial activity of moxalactam and other antibiotics against the Bacteroides fragilis* group and other anaerobic bacteria

Organism	Drug	Cumulative % inhibited at MIC (μg/ml) of:					
		≤1	2	4	8[a]	16	32
Bacteroides fragilis group (94)[b]	Moxalactam	51	74	86	92	96	
	Carbenicillin				52	78	87
	Cefoxitin	29	61	82	95	100	
	Chloramphenicol		11	70	97	100	
	Clindamycin	95	96	98	100		
Bacteroides spp. (48)	Moxalactam	38	44	48	69	79	96
	Carbenicillin				81	85	89
	Cefoxitin	46	63	75	88	96	100
	Chloramphenicol	27	52	88	96	100	
	Clindamycin	97	100				
Clostridium spp. (22)	Moxalactam	64	73	82			
	Carbenicillin				100		
	Cefoxitin	73	82				
	Chloramphenicol	9	41	86	91	100	
	Clindamycin		91		95	100	
Eubacterium spp. (17)	Moxalactam	24	35	53	65	76	
	Carbenicillin				76	82	100
	Cefoxitin	41	47	76	100		
	Chloramphenicol	29	53	88	94	100	
	Clindamycin	82		88			
Fusobacterium spp. (15)	Moxalactam	67	100				
	Carbenicillin				100		
	Cefoxitin	88	100				
	Chloramphenicol	100					
	Clindamycin	100					
Anaerobic gram-positive cocci (46)	Moxalactam	20	37	67	80	83	87
	Carbenicillin				83	87	89
	Cefoxitin	76	78	83	87	91	96
	Chloramphenicol	29	61	96			
	Clindamycin	93		96			
Other anaerobic species (6)[c]	Moxalactam	33	50			100	
	Carbenicillin				100		
	Cefoxitin	33	67	83	100		
	Chloramphenicol	33	83		100		
	Clindamycin	83	100				

[a] Lowest tested concentration of carbenicillin.

[b] Includes (number of isolates): *Bacteroides fragilis* (68), *B. thetaiotaomicron* (8), *B. vulgatus* (12), *B. ovatus* (2), and *B. distasonis* (4).

[c] Includes *Lactobacillus* spp. (4), *Bifidobacterium* spp. (1), and *Veillonella* spp. (1).

ity of all three drugs was poor against most *Streptococcus* species, especially the enterococci. Cefamandole was generally from 4- to >16-fold more active than moxalactam ($P = < 0.001$) against *Streptococcus agalactiae*, *Streptococcus pyogenes*, other beta-streptococci, and the *Streptococcus viridans* group. Among the other gram-positive bacteria, all tested strains of *Listeria monocytogenes* and *Bacillus* species were resistant (>32 μg/ml) to moxalactam, whereas the corynebacteria were generally susceptible to the lower concentrations tested.

Moxalactam demonstrated equal or slightly superior in vitro activity as compared to cefamandole and tobramycin against only three non-*Enterobacteriaceae* species, e.g., *Aeromonas hydrophila*, *Moraxella* sp., and *Pseudomonas maltophilia*. For all other tabulated species and species groups, tobramycin was significantly ($P = < 0.001$) more active than either moxalactam or cefamandole. Though moxalactam *P. aeruginosa* MICs were much lower (mode = 16 μg/ml) than those of cefamandole, only 27.6 and 77.9% of the strains were inhibited at 8 and 32 of moxalactam per ml, respectively.

Moxalactam showed antimicrobial activity similar to that of cefoxitin against most of the 248 strict anaerobes shown in Table 3. Moxalactam inhibited 92% of the tested *Bacteroides fragilis* group strains at ≤8 μg/ml. Against other anaerobes, moxalactam had equal or fourfold less activity when compared with cefoxitin. Two antibiotic-resistant populations of bacteria were also tested against 13 antimicrobial agents (Table 4). The cephalothin-resistant strains were selected from each of the participating laboratories, and their numbers were adjusted to simulate the clinical incidence of cephalothin-resistant isolates. Cefotaxime (72% inhibited at ≤ μg/ml) and moxalactam (69% inhibited at ≤8 μg/ml) were the most active among the "cephalosporins" tested; amikacin (92% inhibited at ≤16 μg/ml) was the most active aminoglycoside; and piperacillin (86% inhibited at ≤64 μg/ml)

TABLE 4. *In vitro comparison of moxalactam and 12 other antibiotics against two populations of antibiotic-resistant bacteria*

Population (no. of isolates)	Drug	MIC_{25}[a] (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Cephalothin resistant (100)[b]	Moxalactam	≤0.125	0.5	32
	Cefotaxime	≤0.125	1	32
	Cefoxitin	8	>64	>64
	Cefamandole	4	64	>64
	Cefazolin	>64	>64	>64
	Ampicillin	64	>256	>256
	Azlocillin	8	32	>256
	Carbenicillin	8	16	>256
	Mezlocillin	4	16	>256
	Piperacillin	4	4	>256
	Ticarcillin	4	16	>256
	Amikacin	2	4	16
	Gentamicin	0.5	1	16
Aminoglycoside resistant (50)[c]	Moxalactam	0.5	4	32
	Cefotaxime	0.5	2	64
	Cefoxitin	4	32	>64
	Cefamandole	2	>64	>64
	Cefazolin	8	>64	>64
	Ampicillin	256	>256	>256
	Azlocillin	16	32	>256
	Carbenicillin	16	64	>256
	Mezlocillin	16	32	>256
	Piperacillin	4	16	>256
	Ticarcillin	8	32	>256
	Amikacin	4	16	256
	Gentamicin			

[a] MIC_{25}, MIC_{50}, MIC_{90}, MICs inhibiting 25, 50, or 90% of isolates tested.

[b] Cephalothin-resistant (MIC, ≥32 μg/ml) bacteria representing those species most commonly found in the clinical population tested (current study).

[c] Gram-negative and gram-positive organisms resistant to kanamycin (MIC, ≥64 μg/ml), gentamicin (MIC, ≥16 μg/ml), tobramycin (MIC, ≥16 μg/ml), any two, or all three.

and mezlocillin (81% inhibited at ≤64 μg/ml) were the most active new penicillins. The aminoglycoside-resistant strains were those obtained from previous studies (7, 8) and others kindly supplied by G. Miller of Schering Corp. and K. Price of Bristol Laboratories. The rank order of in vitro activity against this latter resistant population was piperacillin (68% inhibited at ≤64 μg/ml) > moxalactam (66% inhibited at ≤8 μg/ml > carbenicillin (62% inhibited at ≤128 μg/ml) > mezlocillin (60% inhibited at ≤64 μg/ml) = cefotaxime (60% inhibited at ≤8 μg/ml).

The effect of raising the inoculum concentration from 10^3 to 10^5 colony-forming units per ml was minimal with moxalactam, cefamandole, and tobramycin (not shown). However, MICs of all three antibiotics with an inoculum of 10^7 colony-forming units per ml were generally in the resistant range. The moxalactam and tobramycin MICs were also less affected than those of cefamandole when compared to the results with an inoculum of 10^5 colony-forming units per ml.

Moxalactam possesses potent antimicrobial activity against the *Enterobacteriaceae* and lesser degrees of inhibition against anaerobes, staphylococci, and *P. aeruginosa* (2, 6, 15, 18–20). The spectrum of activity and high potency against the enteric bacilli was similar to those reported for cefatoxime and cefoperazone (3, 6, 10, 14, 20). Moxalactam inhibited 98.9% of the *Enterobacteriaceae* at ≤8 μg/ml, compared to 85.0 and 93.8% for ≤8 μg of cefamandole and ≤4 μg of tobramycin per ml, respectively. Though moxalactam was somewhat active against *P. aeruginosa*, the high modal MIC of 16 μg/ml and incomplete coverage (77.9% of all isolates inhibited at ≤32 μg/ml) cast some doubt on its potential clinical usefulness. Similarly, moxalactam had higher modal MICs aganst both *S. aureus* and *S. epidermidis* than did cefamandole and tobramycin. However, moxalactam inhibited nearly equal numbers (66.6%) of gram-positive organisms at ≤32 μg/ml compared to cefamandole (69.6%) at ≤8 μg/ml.

Moxalactam and cefotaxime appear to offer promise for the treatment of some resistant populations of bacteria prevalent in certain institutions (7, 8, 14). Cefotaxime and moxalactam were among the most active beta-lactams against both the cephalothin- and aminoglycoside-resistant strains. The newer semisynthetic penicillins, piperacillin and mezlocillin, also appear effective against both of these resistant populations.

This 1-oxa-β-lactam antibiotic, moxalactam (LY127935), inhibited 76.8 and 87.2% of all facultative bacteria tested in this series of MICs of ≤8 and ≤32 μg/ml, respectively. This compared favorably with the two most active (on a weight basis) representatives of the currently available aminoglycosides and cephalosporins, e.g., tobramycin and cefamandole. Tobramycin inhibited 82.5% of the isolates at ≤4 μg/ml, and cefamandole inhibited 72.2% of the strains at ≤8 μg/ml. Further in vitro and in vivo investigations are considered appropriate.

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