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Comparison of In Vitro Activity of Moxalactam (LY127935) with Cefazolin, Amikacin, Tobramycin, Carbenicillin, Piperacillin, and Ticarcillin Against 420 Blood Culture Isolates

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To compare the in vitro activity of moxalactam (LY127935), a new broad-spectrum antimicrobial agent, with cefazolin, amikacin, tobramycin, carbenicillin, piperacillin, and ticarcillin, each drug was tested against 420 bacterial isolates from the blood of septic patients. Standard broth dilution methods were used to determine minimum inhibitory and bactericidal concentrations. LY127935 was as active as the aminoglycosides against aerobic gram-negative organisms, including *Pseudomonas aeruginosa*, and was at least 10-fold more active than the other β-lactam agents against these bacteria. LY127935 was the most active agent tested against *Bacteroides fragilis*; its activity against all other anaerobic bacteria and *Staphylococcus aureus* was similar to those of the other agents tested. All streptococci, however, grew at higher concentrations of LY127935 than any other drug, and *Streptococcus faecalis* and *Listeria monocytogenes* were not inhibited at the highest concentration tested (minimum inhibitory concentration, >64 μg/ml). Although a greater proportion of blood culture isolates were susceptible to LY127935 than to any other drug tested, LY127935 does not have a sufficiently broad spectrum of in vitro activity to be recommended safely alone for empirical treatment of sepsis of unknown etiology.

Several new antimicrobial agents have been developed in recent years to provide a nontoxic alternative to available agents for treating resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and anaerobic organisms. Cefamandole and cefoxitin have broader activity in vitro than older cephalosporins, but they are still secondary choices to more established and cheaper drugs (1). Piperacillin (4, 11, 18) and furazlocillin (4, 18) are active in vitro against many aerobic gram-negative rods and anaerobic organisms, but resistant strains occur. SCE-129, a new cephalosporin, is very active against *P. aeruginosa*, but it is not active against other gram-negative rods (8).

Moxalactam (LY127935), a new semisynthetic β-lactam antimicrobial agent, showed extensive in vitro activity against aerobic gram-negative organisms in preliminary studies (G. Brier, H. R. Black, R. S. Griffith, K. S. Israel, and J. W. Wolny, Abstr. Annu. Meet. Am. Soc. Microbiol. 1979, A38, p. 7). LY127935 differs from other β-lactam compounds by the substitution of oxygen for sulfur in the six position of the cepham nucleus. This molecular alteration is thought to account for its enhanced activity, especially against *P. aeruginosa* and the *Bacteroides fragilis* group, and to make it neither a penicillin nor a cephalosporin.

The purpose of this study was to compare the activity of LY127935 with those of amikacin, tobramycin, carbenicillin, piperacillin, ticarcillin, and cefazolin, which are used alone or in combination for treatment of patients with sepsis, against 420 bacterial species isolated from septic patients.

MATERIALS AND METHODS

Microorganisms. We tested 420 blood culture isolates from patients with true bacteremia. At our hospitals an infectious disease consultant reviews all clinical and laboratory data for every patient with positive blood cultures to determine whether the organism isolated represents true sepsis or contamination. Only one isolate of any species from a given episode of true sepsis in the same patient was included. The number of isolates of each bacterial species tested was proportionate to their occurrence in blood at our hospitals. Isolates were suspended in 50% Trypticase soy broth and 50% fetal calf serum with 1% yeast extract and stored at −70°C. Control organisms used throughout this study were *Escherichia coli* (strain ATCC 25922; American Type Culture Collection, Rockville, Md.), *Staphylococcus aureus* (strain ATCC 25923), and *P. aeruginosa* (strain ATCC 27853).

Antibiotics. Standard powders were provided by

their manufacturers as follows: LY127935, lot 51-113-90 and cefazolin, lot 51-766-8E (Eli Lilly and Co., Indianapolis, Ind.); amikacin, lot C7089 (Bristol Laboratories, Syracuse, N.Y.); carbenicillin, lot 7X075 (Pfizer Inc., New York, N.Y.); piperacillin, lot 722385 (American Cyanamid Co., Lederle Laboratories, Pearl River, N.Y.); ticarcillin, lot KT 1767 (Beecham Laboratories, Bristol, Tenn.). Tobramycin was provided in solution, lot 51-103-7B (Eli Lilly and Co.). Antibiotic solutions were prepared in distilled water and stored at −70°C until used. Fresh stock solutions of β-lactam drugs were prepared at monthly intervals.

Broth dilution testing. The minimum inhibitory concentrations (MICs) for all isolates except *Neisseria gonorrhoeae* and *Corynebacterium* spp. were determined in duplicate by a microtiter modification (13) of the method chosen by the International Collaborative Study (3). The final inoculum size was 10^5 to 10^6 bacteria per ml. Most bacterial species were suspended in saline after overnight growth on agar medium, diluted in Mueller-Hinton (MH) broth, and added to an equal volume (50 μl) of MH broth containing serial twofold dilutions of antibiotic. For testing strains of *P. aeruginosa*, 50 mg of calcium and 20 mg of magnesium were added to each liter of the MH broth. For some bacteria an alternative medium was substituted for MH broth: streptococci were tested in Trypticase soy broth, *Haemophilus influenzae* were tested in Schaedler broth with 5% Fildes reagent, and anaerobes were tested in Schaedler broth with added hemin (5 μg/ml) and vitamin K_1 (0.5 μg/ml). Streptococci and *H. influenzae* were incubated in CO_2, anaerobes were incubated in GasPak jars (BBL Microbiology Systems, Cockeysville, Md.), and all others were incubated in ambient air at 35°C. MIC endpoints were read as the lowest dilution of antibiotic with no turbidity. The minimum bactericidal concentration (MBC) for each isolate was determined by subculturing 3 μl from each microtiter well by multipoint inoculator to an antibiotic-free agar plate. MBC endpoints were read as the lowest dilution of antibiotic with no growth (>99.9% killing) after overnight incubation at 35°C.

Agar dilution testing. MICs were determined for *N. gonorrhoeae* and *Corynebacterium* spp. in duplicate by the method used in the International Collaborative Study report (3). *N. gonorrhoeae* were inoculated onto MH agar containing 1% hemoglobin and 1% IsoVitaleX (BBL Microbiology Systems). *Corynebacterium* spp. were inoculated to MH agar containing 5% defibrinated sheep blood. Inocula were suspended in MH broth after overnight incubation on chocolate or blood agar plates, adjusted to a 0.5 McFarland standard, diluted 1:10 in MH broth, and inoculated by multipoint inoculator to antibiotic-containing agar (inoculum size, about 10^4 bacteria). MIC endpoints were accepted as the lowest concentration of antibiotic in which no growth occurred.

RESULTS

The geometric means and range of MICs are presented in Table 1. LY127935 proved as effective in vitro as the aminoglycosides and piperacillin against *P. aeruginosa*, whereas cefazolin was inactive and the other penicillins were active only at high concentrations. LY127935 inhibited all *Enterobacteriaceae* with MICs similar to the aminoglycosides, and with MICs at least 10-fold lower than those of the other drugs, including piperacillin. LY127935 was the most active agent tested against the *B. fragilis* group, and its activity against all other anaerobic organisms was similar to those of the other drugs tested.

Similar concentrations of LY127935, carbenicillin, and ticarcillin inhibited *S. aureus*, whereas cefazolin was 10-fold more active. Streptococci grew at higher concentrations of LY127935 than any of the other agents studied except the aminoglycosides. *Listeria monocytogenes*, enterococci, and *Corynebacterium* spp. grew at the highest concentration of LY127935 tested (64 μg/ml).

Minimal bactericidal concentrations were generally close to MICs with MBC-to-MIC ratios of less than 2 (Tables 1 and 2). Exceptions, expressed as MBC-to-MIC ratios, were: cefazolin against *S. faecalis* (2.1), other streptococci (2.2), and *L. monocytogenes* (2.2); carbenicillin (9.8), piperacillin (2.7), and ticarcillin (5.9) against *L. monocytogenes*; ticarcillin against *Enterobacter* spp. (2.3); and LY127935 (2.4) and piperacillin (2.3) against *P. aeruginosa*.

Achievable concentrations of LY127935 in serum have not been established, but, assuming dosage and pharmacokinetics similar to cephalosporins, organisms may be considered susceptible with MICs of ≤16 μg/ml (2). Based on the National Committee for Clinical Laboratory Standards criteria, MICs of susceptible organisms for the other agents tested are (μg/ml): cefazolin, ≤16; amikacin, ≤16; tobramycin, ≤8; carbenicillin, ≤128 for *P. aeruginosa*, ≤16 for other gram-negative bacilli, ≤2 for *H. influenzae*, and ≤0.12 for other organisms; and pipercillin and ticarcillin, ≤64 for *P. aeruginosa*, ≤16 for other gram-negative bacilli, ≤2 for *H. influenzae*, and ≤0.12 for other organisms (7). Using these endpoints, the percentage of the 420 blood culture isolates inhibited by each drug, tested in proportion to their actual clinical occurrence, was: LY127935, 87; cefazolin, 79; amikacin, 67; tobramycin, 67; carbenicillin, 34; piperacillin, 59; and ticarcillin, 39. The percentage of isolates killed by each drug was: LY127935, 82; cefazolin, 76; amikacin, 64; tobramycin, 65; carbenicillin, 28; piperacillin, 56; and ticarcillin, 29.

DISCUSSION

Our results support the impression that LY127935 has excellent broad-spectrum in vitro activity. LY127935 inhibited and killed a greater proportion of all isolates than any other agent

TABLE 1. *Geometric mean MICs of seven antimicrobial agents against 420 blood isolates by broth dilution testing*

Bacterial species (no. tested)	Geometric mean (range) of MICs (μg/ml)						
	LY127935	Cefazolin	Amikacin	Tobramycin	Carbenicillin	Ticarcillin	Piperacillin
Staphylococcus aureus (52)	4.5 (2–16)	0.7 (0.1–4.0)	1.4 (0.3–8.0)	0.2 (<0.1–>32.0)	6.3 (0.3–32.0)	6.0 (0.3–16.0)	13.6 (0.3–>64)
Staphylococcus epidermidis (14)	14.5 (4–>32)	0.5 (0.1–4.0)	3.8 (0.1–64.0)	0.6 (<0.1–>32)	7.6 (1–64)	6.9 (0.5–64.0)	2.3 (<0.3–32.0)
Enterococci (21)	>64 (64–>64)	25.4 (4–>64)	>64 (32–>64)	>32 (16–>32)	66.1 (16–>256)	66.1 (16–>256)	4.9 (2–>64)
Streptococcus spp. (75)	2.3 (0.3–>64)	0.1 (<0.1–16.0)	>64 (4–>64)	>32 (>32)	0.5 (<0.3–32.0)	0.5 (<0.3–32.0)	0.1 (<0.1–2.0)
Corynebacterium spp.[a] (5)	64 (4–>64)	36.7 (0.3–>64.0)	>64 (8–>64)	>32 (16–>32)	48.5 (1–>64)	48.5 (1–>64)	48.5 (1–>64)
Listeria monocytogenes (7)	>64 (>64)	2.7 (1–8)	1.1 (0.3–8.0)	0.2 (<0.1–2.0)	5.4 (2–32)	4.9 (2–32)	2.7 (2–8)
Escherichia coli (83)	0.1 (<0.1–8.0)	1.7 (0.5–>64)	1.5 (0.1–32.0)	0.7 (<0.1–8.0)	28.5 (4–>256)	18.9 (0.5–>256.0)	4.5 (0.5–>64.0)
Enterobacter spp. (11)	0.3 (<0.1–16.0)	>64 (16–>64)	1.1 (0.3–8.0)	0.4 (0.1–2.0)	10.3 (2–128)	8.0 (1–128)	2.9 (0.5–8.0)
Klebsiella spp. (33)	0.1 (<0.1–0.5)	3.9 (1.0–>64)	0.8 (0.3–4.0)	0.3 (0.1–16.0)	>256 (4–>256)	211.8 (2–>256)	13.0 (2–>64)
Proteus mirabilis (11)	0.1 (<0.1–0.3)	2.9 (1.0–8.0)	2.9 (0.5–8.0)	0.8 (0.5–2.0)	1.1 (0.5–16.0)	0.7 (0.5–4.0)	0.4 (0.3–2.0)
Proteus spp. (IP)[b] (4)	0.1 (0.1)	>64 (64–>64)	1.2 (0.5–2.0)	1.4 (0.5–4.0)	0.8 (0.5–1.0)	1.4 (0.5–4.0)	0.7 (0.3–2.0)
Serratia marcescens (11)	1.0 (0.3–8.0)	>64 (>64)	2.1 (0.5–32.0)	3.3 (1–32)	30.0 (4–>256)	16.0 (4–>256)	4.8 (1–32)
Acinetobacter calcoaceticus (4)	32.0 (16–64)	>64 (8–>64)	5.7 (1–32)	1.7 (0.1–8.0)	11.3 (2–32)	6.7 (2–16)	8.0 (2–16)
Pseudomonas aeruginosa (28)	16.0 (8–32)	>64 (>64)	8.2 (2–64)	1.9 (0.5–8.0)	64.0 (8–>256)	32.8 (8–>256)	9.1 (4–>64)
Neisseria gonorrhoeae[a] (6)	<0.1 (<0.1)	0.5 (0.3–1.0)	—[c]	—	<0.1 (<0.1)	<0.1 (<0.1)	<0.1 (<0.1)
Haemophilus influenzae (4)	0.2 (<0.1–32.0)	>64 (1–>64)	2.8 (2–4)	3.4 (2–4)	4.0 (2–16)	2.8 (2–8)	<0.1 (<0.1)
Gram-positive anaerobic rods (13)	1.9 (0.3–>64.0)	1.0 (<0.1–>64.0)	23.2 (<0.1–>64.0)	12.9 (0.1–>32.0)	1.4 (0.1–>256.0)	1.6 (<0.1–>256.0)	0.8 (<0.1–>64.0)
Gram-positive anaerobic cocci (11)	0.2 (<0.1–>64.0)	0.1 (0.1–>64.0)	14.1 (4–>64)	9.7 (1–>32)	0.2 (<0.1–>256.0)	0.2 (<0.1–>256.0)	0.1 (<0.1–>64.0)
Gram-negative anaerobes (15)	0.7 (<0.1–8.0)	0.3 (<0.1–64.0)	22.6 (2–>64)	18.6 (1–>32)	1.1 (<0.1–32.0)	1.1 (<0.1–16.0)	1.1 (<0.1–>64.0)
Bacteroides fragilis group (13)	1.6 (0.3–8.0)	16.0 (2–>64)	>64 (>64)	>32 (>32)	23.2 (4–256)	28.8 (4–>256)	16.0 (4–>64)

[a] Tested by agar dilution technique.
[b] IP, Indole positive.
[c] —, Not tested.

TABLE 2. *Geometric mean MBCs of seven antimicrobial agents against 409 blood isolates by broth dilution testing*

Bacterial species (no. tested)	Geometric mean (range) of MBCs (μg/ml)						
	LY127935	Cefazolin	Amikacin	Tobramycin	Carbenicillin	Ticarcillin	Piperacillin
Staphylococcus aureus (52)	6.1 (2–32)	0.8 (0.1–4.0)	1.6 (0.5–16.0)	0.2 (<0.1–>32.0)	7.6 (0.3–64.0)	7.5 (0.3–32.0)	15.0 (0.1–>64.0)
Staphylococcus epidermidis (14)	17.7 (4–>32)	0.6 (0.1–4.0)	5.4 (0.1–64.0)	0.8 (0.1–>32.0)	9.3 (1–64)	8.4 (0.5–>64.0)	3.5 (0.5–32.0)
Enterococci (21)	>64 (>64)	52.5 (4–>64)	>64 (32–>64)	>32 (16–>32)	112.1 (16–>256)	108.5 (16–>256)	7.5 (2–>64)
Streptococcus spp. (75)	3.4 (0.5–>64.0)	0.2 (<0.1–>64.0)	>64 (>64)	>32 (>32)	0.7 (<0.3–>64.0)	0.7 (<0.3–>64.0)	0.1 (<0.1–4.0)
Listeria monocytogenes (7)	>64 (>64)	5.9 (4–16)	2.0 (0.5–16.0)	0.3 (<0.1–2.0)	52.5 (4–128)	29.0 (4–128)	7.2 (4–32)
Escherichia coli (83)	0.1 (<0.1–8.0)	2.4 (0.1–>64.0)	1.7 (0.3–32.0)	0.9 (0.1–16.0)	34.2 (2–>256)	22.5 (1–>256)	5.2 (1–>64)
Enterobacter spp. (11)	0.4 (<0.1–16.0)	>64 (16–>64)	1.5 (0.3–8.0)	0.6 (0.1–4.0)	14.1 (2–128)	18.1 (2–256)	5.5 (1–32)
Klebsiella spp. (33)	0.1 (<0.1–1.0)	5.8 (1–>64)	1.0 (0.3–4.0)	0.4 (0.1–>32.0)	>256 (4–>256)	255.9 (2–>256)	18.9 (2–>64)
Proteus mirabilis (11)	0.1 (<0.1–0.3)	2.9 (1–8)	2.7 (0.5–8.0)	0.9 (0.3–4.0)	1.1 (0.5–16.0)	0.7 (0.1–4.0)	0.4 (0.1–2.0)
Serratia marcescens (11)	1.2 (0.5–16.0)	>64 (>64)	3.3 (0.5–64.0)	5.8 (1–32)	53.0 (8–>256)	26.5 (4–>256)	7.1 (1–>64)
Proteus spp. (IP)[a] (4)	0.2 (0.1–0.3)	>64 (>64)	1.7 (1–2)	3.4 (1–16)	1.4 (1–2)	2.4 (0.5–8.0)	1.0 (0.5–2.0)
Acinetobacter calcoaceticus (4)	>64 (32–>64)	>64 (>64)	6.7 (2–32)	2.4 (0.1–16.0)	32.0 (4–128)	19.0 (2–64)	11.3 (4–16)
Pseudomonas aeruginosa (28)	38.0 (16–>64)	>64 (>64)	15.6 (4–>64)	3.1 (1–8)	107.6 (16–>256)	52.5 (32–>256)	21.0 (4–>64)
Haemophilus influenzae (4)	1.4 (<0.1–32.0)	32.0 (16–>64)	4.0 (2–8)	4.8 (2–8)	6.7 (2–32)	4.0 (2–16)	0.2 (<0.1–1.0)
Gram-positive anaerobic rods (13)	2.1 (0.3–>64.0)	0.9 (0.1–>64.0)	25.8 (0.1–>64.0)	12.9 (0.1–>32.0)	1.2 (0.1–>256.0)	1.5 (0.1–>256.0)	0.6 (<0.1–>64.0)
Gram-positive anaerobic cocci (11)	0.2 (<0.1–2.0)	0.1 (<0.1–0.5)	17.0 (8–64)	13.2 (2–>32)	0.3 (<0.3–8.0)	0.2 (<0.1–16.0)	0.1 (<0.1)
Bacteroides fragilis group (13)	2.9 (0.5–>64.0)	27.3 (4–>64)	>64 (>64)	>32 (>32)	46.5 (8–>256)	44.1 (8–>256)	19.8 (4–>64)
Gram-negative anaerobes (14)	0.9 (<0.1–16.0)	0.5 (<0.1–32.0)	27.6 (2–>64)	18.6 (1–>32)	1.3 (<0.3–8.0)	1.5 (<0.3–16.0)	1.1 (<0.1–>64.0)

[a] IP, Indole positive.

we tested. This greater activity is especially important in that we tested only organisms that caused documented clinical sepsis in proportion to their actual frequency of isolation at our hospitals. This proportion is quite comparable to that which has been previously reported in both teaching (17) and community hospitals elsewhere (5, 10) and in patients with bacteremia complicating neoplastic disease (12). In a similar study testing the same 420 bacterial isolates at our hospital against cefamandole, cefoxitin, gentamicin, and ampicillin, cefamandole demonstrated the widest spectrum of in vitro activity (S. Mirrett and L. B. Reller, unpublished data). However, LY127935 still inhibited a greater number of isolates tested.

LY127935 demonstrated excellent in vitro activity against all aerobic gram-negative organisms, including *P. aeruginosa*. The MICs of LY127935 and the aminoglycosides were similar for all the organisms. As shown by others, the activity of piperacillin against *P. aeruginosa* was also similar to those of LY127935 and the aminoglycosides (6, 11, 18). However, LY127935 was 10-fold or more active than piperacillin against other aerobic gram-negative rods.

LY127935 performed well against all anaerobic organisms, especially the *Bacteroides fragilis* group, with the lowest MICs of the agents tested. Previous studies have shown carbenicillin and ticarcillin to be suitable agents for treating anaerobic infections (9, 14–16). Given the greater in vitro activity of LY127935, especially against *Bacteroides* spp., it may provide a useful clinical alternative.

Against gram-positive organisms, however, LY127935 showed less activity. Importantly, all enterococci, *L. monocytogenes*, and *Corynebacterium* spp. were resistant in vitro.

In summary, LY127935 offers a broad spectrum of antimicrobial coverage in vitro. However, 13% of all bacteria tested were not inhibited by LY127935.

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