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In Vitro Activity of L-627, a New Carbapenem

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The in vitro activity of L-627, a new parenterally administered carbapenem, was compared with those of imipenem, meropenem, FCE 22101 (a penem), ceftazidime, and ceftriaxone. L-627 was active against members of the family *Enterobacteriaceae* (MIC for 90% of strains tested [MIC_{90}] ranging from 0.03 to 4 μg/ml). L-627 displayed activity equal to that of meropenem against *Pseudomonas aeruginosa* (MIC_{90}, 2 μg/ml), although, as with other carbapenems, the antipseudomonal activity was reduced against D2-deficient strains. Staphylococci and streptococci were susceptible (MIC_{90} of 1.0 μg/ml for *Staphylococcus aureus* and 0.015 μg/ml for group A streptococci). L-627 also had activity against anaerobic bacteria (MIC_{90}, 2.0 μg/ml for *Bacteroides fragilis*). *Neisseria gonorrhoeae* and *Neisseria meningitidis* were highly susceptible (MIC_{90}, 0.06 μg/ml), and against the common respiratory pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*), the MIC_{90}s were ≤2.0 μg/ml. The protein binding of L-627 ranged from 13.8 to 22%, depending on the concentration. The presence of human serum had little effect on the MIC or MBC of L-627. These results suggest that L-627 merits further study in the treatment of infections caused by a wide range of pathogens.

L-627 (LJC 10,627) {(1*R*,5*S*,6*S*)-2-[(6,7-dihydro-5H-pyrazolol[1,2-α][1,2,4,]triazolium-6-yl)]thio-6-[(*R*)-1-hydroxyethyl]-1-methyl-carbapenem-3-carboxylate} is a new injectable carbapenem which, unlike imipenem, has a methyl group at the 1-β position which confers stability against hydrolysis by kidney dehydropeptidase 1 (7, 9). Administration with a dehydropeptidase inhibitor is therefore unnecessary. Previous studies (3, 7, 9, 11) have shown L-627 to have a broad antibacterial activity. In this study, the in vitro activity of L-627 was compared with those of carbapenems, a penem (FCE 22101), and other antibiotics against a range of aerobic and anaerobic organisms.

Imipenem is thought to penetrate the outer membrane of gram-negative organisms via porin proteins (1, 2, 8, 10). It has been shown that the resistance of *Pseudomonas aeruginosa* to imipenem (and other penems and carbapenems) is associated with depletion of an outer membrane protein D2 (molecular weight, 45,000 to 49,000), which facilitates the diffusion of imipenem into the cell (1, 2). In this study, the MICs of L-627 and other antimicrobial agents, including imipenem, against D2-deficient strains of *P. aeruginosa* were compared with those for strains containing normal levels of this protein.

MATERIALS AND METHODS

Strains and antimicrobial agents. A total of 665 strains were studied, including 606 recent clinical isolates collected over the past 18 months. The remaining 59 strains comprised transconjugants possessing characterized β-lactamases and strains known to be resistant to imipenem. Strains had previously been identified by routine laboratory methods and stored at −70°C. Expression of the outer membrane protein D2 in selected strains of *P. aeruginosa* was determined following probing of the outer membrane with anti-D2 antibody (2) and sodium dodecyl sulfate-polyacrylamide gel electrophoresis with 10 and 14% polyacrylamide gels (4). Antimicrobial agents were obtained from the following sources: L-627 from Lederle Laboratories, Pearl River, N.J.; ceftazidime from Glaxo Laboratories, Greenford, United Kingdom; ceftriaxone from Roche Products Ltd., Hertsfordshire, United Kingdom; imipenem from Merck Sharp and Dohme Ltd., Hertfordshire, United Kingdom; meropenem from ICI, Macclesfield, United Kingdom; FCE 22101, a penem, from Farmitalia Carlo Erba, St. Albans, United Kingdom; and benzylpenicillin from SmithKline Beecham Pharmaceuticals, Surrey, United Kingdom.

MICs. MICs were determined by an agar dilution method. Modified Iso-Sensitest agar (CM885B; Oxoid, Basingstoke, United Kingdom) was used for aerobic organisms and was supplemented with 20 μg of NAD per ml (BDH Chemicals, Poole, United Kingdom) and 5% horse blood for fastidious strains. Wilkens and Chalgren agar (Oxoid) with the addition of 5% horse blood was used for testing anaerobes.

Inocula were prepared as follows. Fastidious organisms were grown in brain heart infusion broth (Oxoid) supplemented with 20 μg of NAD per ml and 5% horse blood, anaerobic organisms were grown in Wilkens and Chalgren broth (Oxoid), and all other strains were grown in digest broth (Southern Group, London, United Kingdom). All organisms were grown to yield a final viable count of 10^9 organisms per ml after overnight incubation.

A final inoculum of 10^4 CFU was obtained by diluting overnight broth culture 1:100 and then transferring 1 μl of the diluted culture to the surface of the agar plates with a multipoint inoculator (Denley-Tech, Billingshurst, United Kingdom).

After inoculation, plates were incubated for 18 to 24 h in air at a temperature of 35 to 37°C, except for fastidious strains, which were incubated in an atmosphere of 4% carbon dioxide in air, and anaerobes, which were incubated in an anaerobic cabinet (Don Whitley, Skipton, United Kingdom) for 48 h.

The MIC was defined as the concentration at which no more than 10 colonies were detected.

Determination of MBC and effect of serum on the activity of L-627. MBCs and the effect of serum on activity were determined for two strains each of *Escherichia coli*, *Klebsiella* spp., *Enterobacter cloacae*, *P. aeruginosa*, and *Staphylococcus aureus*, by using a modification of the method of Pearson et al. (7). Concentrations of L-627 were prepared in

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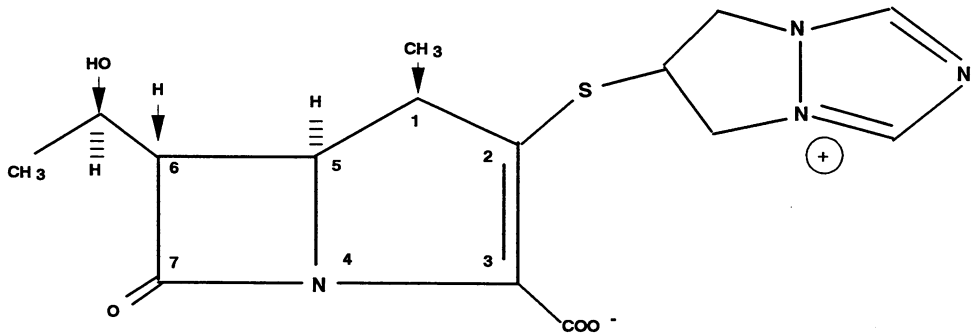

FIG. 1. Structure of L-627.

Iso-Sensitest broth (CM473) and broth containing 20 and 70% human serum (Bradsure Biologicals, Market Harborough, United Kingdom). Overnight broth cultures of the above strains were diluted, and the dilution was used to inoculate the broth to give a final concentration of 10^5 CFU/ml. After overnight incubation at 35 to 37°C, the MIC was determined as the concentration of drug at which there was no visible growth. The 99.9% lethality was determined by subculture of 0.1 ml into antibiotic-free Iso-Sensitest and further incubation.

Protein binding. Protein binding of L-627 was determined by using a micropartition system (Centrifree System; Amicon, Beverly, Mass.). Concentrations of 5, 50, and 100 μg of L-627 per ml were prepared in pooled human serum (Bradsure Biologicals). After centrifugation, protein-free extracts were assayed against standards prepared in phosphate buffer (pH 7) by using Iso-Sensitest agar and *E. coli* NCTC 10418 as the indicator organism. The lower limit of sensitivity of the assay was 0.12 μg/ml.

RESULTS

The activities of L-627 (Fig. 1) and the other antibiotics under study are shown in Table 1. L-627 was highly active against strains of the *Enterobacteriaceae*, especially the more common clinically significant isolates (e.g., *E. coli*, *Klebsiella* spp., and *Proteus mirabilis*). Activities were generally twofold greater than those of imipenem but similar to or less than those of meropenem, particularly against organisms which commonly possess a chromosomal β-lactamase (e.g., *Enterobacter* spp. and *Morganella* and *Serratia* spp.). Ceftriaxone was twofold more active than L-627 against *E. coli* and *Klebsiella* spp. but less active against *Enterobacter* and *Serratia* spp. FCE 22101 was the least active of the carbapenem and penem groups against these strains.

L-627 was as active as meropenem against *P. aeruginosa* (MIC_{90}, 2 μg/ml) and more active than the other agents tested, being twofold more active than ceftazidime; no useful activity was shown by FCE 22101 or ceftriaxone. When tested against strains of *P. aeruginosa* known to have normal expression of outer membrane protein D2, L-627 and the other carbapenems were active at concentrations of ≤4 μg/ml. However, for D2-deficient strains, a corresponding decrease in susceptibility was observed, with the lowest activity being demonstrated against D2-negative strains (Table 2).

Ceftazidime had modest activity against *Xanthomonas maltophilia* (MIC_{90}, 8 μg/ml), whereas the other agents were inactive.

Neisseria spp. were highly susceptible to L-627, the MIC_{90} being 0.06 μg/ml for *N. meningitidis* and *N. gonorrhoeae*; ceftriaxone was the most active agent, being 16-fold more active against *N. gonorrhoeae* and 32-fold more active against *N. meningitidis* than L-627. Three of the isolates of *N. gonorrhoeae* were resistant (MIC, >1 μg/ml) to penicillin (β-lactamase producers), but all were susceptible to the other agents studied.

The activity of L-627 against *Haemophilus influenzae* (which included 20 β-lactamase-producing strains) was similar to that of imipenem and FCE 22101, with ceftriaxone and ceftazidime being generally more active. However, against *Moraxella catarrhalis* (22 of 30 strains were β-lactamase producers), L-627 was less active, meropenem having 16-fold greater activity.

Against the *Staphylococcus* spp., L-627 was more active than the cephalosporins, but the new agent was fourfold less active than imipenem, particularly against *S. aureus* and *S. saprophyticus*. Activity of L-627 against the methicillin-resistant *S. aureus* strains was reduced (MICs, 1 to 8 μg/ml). This decreased activity was seen with all agents under study, and there was no useful activity of the cephalosporins against these strains. With the streptococci, L-627 again displayed considerable activity, with MICs similar to those of penicillin against *S. pyogenes*. The strains of *S. pneumoniae* included two strains resistant to penicillin (MIC, >0.25 μg/ml); imipenem and L-627 showed MICs of 0.12 and 0.25 μg/ml, respectively. Against the enterococci, all agents displayed reduced activities, especially against *Enterococcus faecium*, with all drugs tested having no useful activity.

Activity against anaerobic bacteria was measured against strains of *Bacteroides fragilis* and *Peptostreptococcus* spp. L-627 was active but was up to fourfold less active than imipenem, although it was fourfold more active than meropenem. The cephalosporins showed no useful activity against *B. fragilis*.

The presence of serum did not affect the MIC of L-627 against the majority of strains tested (Table 3), although there was an eightfold rise in the MIC with 70% human serum from that seen with 20% human serum for one strain of *S. aureus*. There was also a marked rise in the MBC with 70% human serum for one strain of *P. aeruginosa*.

The results of the studies of the activity of L-627 against the transconjugant strains possessing known β-lactamases are shown in Table 4. L-627 was highly active against strains with TEM-1, TEM-2, TEM-3, TEM-5, TEM-9, OXA-1,

TABLE 1. The activity of L-627 compared with those of other agents

Organism(s) (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
Escherichia coli (50)	L-627	0.03	0.03	0.004–0.25
	Imipenem	0.06	0.12	0.015–0.25
	Meropenem	0.015	0.03	0.008–0.03
	FCE 22101	0.5	0.5	0.25–1
	Ceftazidime	0.06	0.12	0.03–4
	Ceftriaxone	0.015	0.06	0.008–0.5
Klebsiella spp. (50)	L-627	0.06	0.25	0.03–0.5
	Imipenem	0.12	0.12	0.06–0.25
	Meropenem	0.03	0.03	0.03
	FCE 22101	0.5	1	0.5–4
	Ceftazidime	0.06	0.5	0.015–1
	Ceftriaxone	0.03	0.25	0.002–0.5
Citrobacter spp. (9)	L-627	0.06	0.25	0.03–0.5
	Imipenem	0.12	0.25	0.06–0.25
	Meropenem	0.03	0.03	0.03
	FCE 22101	1	4	0.5–4
	Ceftazidime	0.12	4	0.03–32
	Ceftriaxone	0.06	1	0.03–4
Serratia spp. (19)	L-627	0.25	1	0.06–1
	Imipenem	0.12	0.5	0.12–2
	Meropenem	0.03	0.03	0.03–0.12
	FCE 22101	8	16	1–16
	Ceftazidime	0.25	2	0.06–2
	Ceftriaxone	1	32	0.03–32
Proteus mirabilis (48)	L-627	1	2	0.12–4
	Imipenem	1	2	0.12–4
	Meropenem	0.06	0.06	0.03–0.12
	FCE 22101	2	2	1–2
	Ceftazidime	0.03	0.06	0.015–2
	Ceftriaxone	0.004	0.008	0.004–0.06
Morganella morganii (29)	L-627	1	2	0.12–2
	Imipenem	2	4	0.5–4
	Meropenem	0.03	0.06	0.03–0.06
	FCE 22101	4	4	2–8
	Ceftazidime	0.03	0.5	0.015–16
	Ceftriaxone	0.004	0.06	0.004–8
Proteus vulgaris (22)	L-627	1	4	0.12–4
	Imipenem	2	4	0.12–4
	Meropenem	0.03	0.06	0.03–0.06
	FCE 22101	1	2	1–4
	Ceftazidime	0.03	0.06	0.015–0.06
	Ceftriaxone	0.06	0.12	0.004–0.25
Enterobacter spp. (30)	L-627	0.12	0.5	0.015–1
	Imipenem	0.12	0.25	0.06–0.5
	Meropenem	0.03	0.12	0.03–0.25
	FCE 22101	4	16	1–16
	Ceftazidime	0.25	32	0.03–64
	Ceftriaxone	0.25	32	0.015–64
Providencia spp. (10)	L-627	2	2	0.25–2
	Imipenem	2	4	0.25–4
	Meropenem	0.12	0.12	0.03–0.12
	FCE 22101	2	2	1–4
	Ceftazidime	0.12	0.25	0.12–0.25
	Ceftriaxone	0.015	0.03	0.008–0.12
Acinetobacter spp. (12)	L-627	0.12	0.25	0.03–16
	Imipenem	0.12	0.25	0.015–8
	Meropenem	0.12	1	0.03–16
	FCE 22101	1	4	0.03–8
	Ceftazidime	2	16	0.015–>128
	Ceftriaxone	4	64	0.008–>128

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TABLE 1—*Continued*

Organism(s) (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
Xanthomonas maltophilia (12)	L-627	>128	>128	0.25–>128
	Imipenem	>128	>128	2–>128
	Meropenem	16	>128	2–>128
	FCE 22101	>128	>128	8–>128
	Ceftazidime	2	8	0.5–128
	Ceftriaxone	64	>128	2–>128
Pseudomonas aeruginosa (50)	L-627	0.5	2	0.12–4
	Imipenem	1	2	0.5–64
	Meropenem	0.5	2	0.06–8
	FCE 22101	128	128	32–>128
	Ceftazidime	1	8	0.5–64
	Ceftriaxone	8	32	1–>128
Staphylococcus aureus (35) (including 5 methicillin-resistant strains)	L-627	0.06	1	0.03–8
	Imipenem	0.015	0.25	0.008–8
	Meropenem	0.06	1	0.03–8
	FCE 22101	0.12	0.5	0.06–1
	Ceftazidime	8	32	4–>128
	Ceftriaxone	2	16	1–>128
Staphylococcus saprophyticus (18)	L-627	0.06	0.12	0.06–0.25
	Imipenem	0.015	0.03	0.015–0.03
	Meropenem	0.12	0.25	0.12–0.25
	FCE 22101	0.12	0.12	0.12
	Ceftazidime	8	16	4–32
	Ceftriaxone	8	8	2–16
Staphylococcus epidermidis (18)	L-627	0.06	0.12	0.015–0.25
	Imipenem	0.008	0.03	0.004–8
	Meropenem	0.12	0.12	0.03–0.25
	FCE 22101	0.06	0.12	0.03–0.12
	Ceftazidime	4	4	0.5–4
	Ceftriaxone	1	4	0.5–8
Group A streptococci (4)	L-627	0.004	0.015	0.004–0.015
	Imipenem	0.004	0.008	0.004–0.008
	Meropenem	0.004	0.004	0.004
	FCE 22101	0.06	0.06	0.06
	Ceftazidime	0.12	0.12	0.06–0.12
	Ceftriaxone	0.015	0.06	0.015–0.06
	Penicillin	0.004	0.008	0.004–0.008
Group B streptococci (4)	L-627	0.06	0.06	0.06
	Imipenem	0.015	1	0.008–1
	Meropenem	0.03	0.03	0.03
	FCE 22101	0.12	0.12	0.12
	Ceftazidime	0.5	0.5	0.25–0.5
	Ceftriaxone	0.06	0.06	0.03–0.06
	Penicillin	0.015	0.015	0.015
Enterococcus faecalis (10)	L-627	2	>128	0.03–>128
	Imipenem	0.5	128	0.5–>128
	Meropenem	2	128	0.008–128
	FCE 22101	4	64	0.06–128
	Ceftazidime	>128	>128	0.25–>128
	Ceftriaxone	128	>128	0.008–>128
	Penicillin	1	64	0.004–128
Streptococcus pneumoniae (18)	L-627	0.015	0.03	0.008–0.25
	Imipenem	0.004	0.015	0.004–0.12
	Meropenem	0.008	0.06	0.004–0.5
	FCE 22101	0.03	0.06	0.03–1
	Ceftazidime	0.25	0.25	0.06–16
	Ceftriaxone	0.015	0.12	0.008–8
	Penicillin	0.008	0.06	0.004–1

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TABLE 1—*Continued*

Organism(s) (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		50%	90%	Range
Streptococcus milleri (13)	L-627	0.06	0.12	0.06–0.12
	Imipenem	0.015	0.06	0.015–0.06
	Meropenem	0.06	0.06	0.03–0.12
	FCE 22101	0.12	0.25	0.06–0.25
	Ceftazidime	8	8	1–16
	Ceftriaxone	0.25	0.25	0.12–0.25
	Penicillin	0.015	0.12	0.008–0.12
Haemophilus influenzae (35) (including 20 β-lactamase-producing strains)	L-627	0.5	2	0.12–4
	Imipenem	0.5	1	0.12–2
	Meropenem	0.06	0.12	0.03–0.12
	FCE 22101	0.5	1	0.03–1
	Ceftazidime	0.12	0.25	0.03–0.25
	Ceftriaxone	0.004	0.015	≤0.002–0.03
	Penicillin	8	32	0.25–64
Moraxella catarrhalis (30) (including 22 β-lactamase-producing strains)	L-627	0.06	0.06	0.06–1
	Imipenem	0.03	0.03	0.008–0.5
	Meropenem	0.004	0.004	≤0.002–0.12
	FCE 22101	0.25	0.5	0.03–1
	Ceftazidime	0.03	0.12	0.015–0.25
	Ceftriaxone	0.06	0.5	0.008–1
	Penicillin	2	8	0.015–16
Neisseria gonorrhoeae (24) (including three β-lactamase-producing strains)	L-627	0.06	0.06	0.03–0.12
	Imipenem	0.03	0.12	0.015–0.12
	Meropenem	0.004	0.015	0.004–0.015
	FCE 22101	0.03	0.12	0.015–0.25
	Ceftazidime	0.03	0.06	0.008–0.25
	Ceftriaxone	≤0.002	0.004	≤0.002–0.015
	Penicillin	0.06	2	0.004–16
Neisseria meningitidis (19)	L-627	0.06	0.06	0.03–0.06
	Imipenem	0.03	0.03	0.015–0.12
	Meropenem	0.004	0.004	0.004–0.008
	FCE 22101	0.015	0.03	0.015–0.03
	Ceftazidime	0.015	0.015	0.008–0.03
	Ceftriaxone	≤0.002	≤0.002	≤0.002
	Penicillin	0.015	0.03	0.008–0.06
Bacteroides fragilis (23)	L-627	0.25	2	0.25–4
	Imipenem	0.06	1	0.03–2
	Meropenem	2	8	0.06–16
	FCE 22101	0.06	4	0.03–4
	Ceftazidime	64	>128	16–>128
	Ceftriaxone	16	>128	4–>128
Peptostreptococci (14)	L-627	0.25	2	0.03–4
	Imipenem	0.03	0.12	0.008–1
	Meropenem	0.12	0.5	0.015–2
	FCE 22101	0.06	1	0.015–2
	Ceftazidime	1	32	0.25–64
	Ceftriaxone	0.5	16	0.25–64

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.

OXA-2, OXA-3, and the broad-spectrum chromosomal enzyme K1. Activity was also preserved against strains of *Enterobacter* spp. and *Citrobacter* spp. possessing derepressed chromosomal β-lactamase. MICs of L-627 against these organisms were lower than those of all other agents tested, the cephalosporins being less active than the carbapenems. Against strains of *P. aeruginosa* possessing PSE-3 and PSE-4 β-lactamases, L-627 was fourfold and eightfold more active, respectively.

Protein binding of L-627 was low. At assigned concentrations of 5, 50, and 100 μg/ml, binding was 13.8, 10.4, and 22.3%, respectively.

DISCUSSION

The results of this study show L-627 to have a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic organisms. The results are in general agreement with those of previous preliminary in vitro studies (3, 5, 9, 10).

TABLE 2. Effect of D2 expression on activity against *P. aeruginosa* (inoculum of 10^6 CFU)

Strain characteristic	Strain no.	MIC (μg/ml) of:						
		L-627	Ceftriaxone	Ceftazidime	Imipenem	Meropenem	FCE 22101	Ciprofloxacin
D2 positive	102	1	8	1	1	4	128	0.5
	182	0.25	4	1	2	0.25	64	1
	211	1	32	2	2	1	128	0.12
	314	0.5	16	2	1	1	128	0.12
	321	0.5	167	2	1	1	>128	0.25
	322	0.5	16	2	1	1	>128	0.25
D2 reduced	150	1	16	2	2	1	>128	8
	151	2	16	2	4	16	>128	4
	195	8	4	2	16	4	128	1
	196	2	4	2	2	4	128	0.5
	62	32	>128	64	16	32	128	>8
D2 negative	123	8	8	1	16	4	128	0.25
	152	8	32	4	16	32	>128	0.5
	167	128	32	4	16	32	>128	1
	168	4	32	4	16	32	>128	0.5
	169	4	32	4	16	32	>128	0.5
	193	8	16	2	8	8	128	0.12
	232	2	8	2	4	8	128	0.12
	266	>128	64	2	128	16	>128	0.5
	280	>128	64	4	128	32	>128	2

Against strains of the *Enterobacteriaceae*, especially the most frequently encountered clinical isolates, L-627 displayed activity similar to that of imipenem but generally was less active than meropenem.

L-627 was active against *P. aeruginosa*. The finding that the MIC rises markedly with loss of the D2 protein from the outer cell wall is consistent with previous observations for imipenem and other related compounds (1, 2), suggesting that L-627 penetrates the outer cell wall of *P. aeruginosa* in a similar fashion. This has previously been shown to be a function of the charge of the variable group linked to C-2 of penem and carbapenem molecules (6)—positively charged moieties utilize the D2 channel. Thus, L-627 would be predicted to penetrate bacterial cells by this route, as it has a positive charge at this site.

The activity against gram-positive pathogens was similar to or slightly less than that of imipenem but marginally greater than that of meropenem. Against all groups of streptococci and staphylococci, the carbapenems and FCE 22101 showed greater activity than the cephalosporins.

The activity of L-627 against the anaerobes tested was slightly lower than that of imipenem. This is in contrast to the findings of Ubukata et al. (9), who found L-627 to be twice as active as imipenem.

In our studies of strains possessing known β-lactamases, we confirm that L-627 is not hydrolyzed by TEM-1, P-99, PC-1, or PSE-1 to PSE-4 (3). L-627 appears to share this property with imipenem against the range of β-lactamases tested, showing lower MICs against derepressed chromosomally mediated β-lactamase-producing strains.

Activity against the common respiratory pathogens *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* was high, as

TABLE 3. Effect of serum on activity of L-627

Organism[a]	L-627 concn (μg/ml) in Iso-Sensitest broth					
	Alone		With 20% human serum		With 70% human serum	
	MIC	MBC	MIC	MBC	MIC	MBC
Escherichia coli	0.5	1	1	2	0.25	1
	0.12	2	0.5	1	0.12	0.5
Klebsiella sp.	1	4	2	2	0.5	0.5
	1	4	2	2	1	2
Enterobacter cloacae	0.5	1	1	4	0.5	4
	0.25	2	0.25	2	0.5	2
Pseudomonas aeruginosa	0.5	1	0.5	1	0.25	1
	0.5	2	0.5	4	0.5	>16
Staphylococcus aureus	0.12	0.5	0.06	0.12	0.25	1
	0.12	0.5	0.03	0.25	0.25	1

[a] Two strains of each organism were tested.

TABLE 4. Activities of L-627 and other agents against strains possessing characterized β-lactamases

Organism	β-Lactamase	MIC (μg/ml) of:					
		L-627	Ceftazidime	Imipenem	Ceftriaxone	Meropenem	FCE 22101
E. coli 1193E	TEM-1	0.03	0.12	0.06	0.06	0.03	0.5
E. coli 1725	TEM-2	0.06	0.25	0.06	0.06	0.03	0.5
E. coli 3455E	TEM-3	0.03	8	0.06	4	0.03	0.5
K. aerogenes H278	TEM-5	0.06	32	0.06	4	0.03	1
E. coli 2639E	TEM-9	0.06	128	0.06	4	0.03	1
E. coli 1527ER	OXA-1	0.03	0.03	0.06	0.015	0.03	0.5
E. coli 2139E	OXA-2	0.06	0.12	0.12	0.03	0.03	0.5
E. coli 2140E	OXA-3	0.06	0.12	0.06	0.03	0.03	0.5
K. pneumoniae H186	K1+	0.25	0.25	0.25	8	0.03	1
K. pneumoniae H187	K1−	0.25	0.06	0.25	0.015	0.03	1
P. aeruginosa 9328	PSE-3	0.25	1	1	8	0.5	128
P. aeruginosa 9333	PSE-4	0.5	0.5	4	4	0.5	128
P. aeruginosa G182	Cephalosporinase[a]	0.25	1	0.5	8	0.25	64
P. aeruginosa G183	Cephalosporinase[b]	0.5	8	1	>128	0.06	128
E. aerogenes K302	Cephalosporinase[a]	0.06	1	0.5	8	0.25	32
E. aerogenes K303	Cephalosporinase[b]	0.03	1	4	8	0.25	64
E. cloacae K298	Cephalosporinase[a]	0.06	0.12	1	8	0.5	64
E. cloacae K299	Cephalosporinase[b]	0.12	32	0.25	8	0.5	32
Citrobacter freundi K294	Cephalosporinase[a]	0.03	0.12	0.12	0.25	0.03	2
Citrobacter freundi K295	Cephalosporinase[b]	0.12	128	0.12	64	0.03	2

[a] Chromosomal cephalosporinase, parent strain.
[b] Chromosomal cephalosporinase, stably derepressed mutant.

it was against *N. gonorrhoeae* and *N. meningitidis*, although activity against *H. influenzae* was much lower than that of ceftriaxone.

Limited studies have shown L-627 to be well tolerated in humans (5), and studies of animals have demonstrated in vivo effectiveness (7). Early pharmacokinetic studies suggest that L-627 has characteristics similar to those of the other carbapenems (5a). The results of this study support further investigation of this compound for clinical use as a potent broad-spectrum antibacterial agent.

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