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In Vitro Activity of MDL 62,879 (GE2270 A) against Aerobic Gram-Positive and Anaerobic Bacteria

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The in vitro activity of MDL 62,879, a new peptide antibiotic that inhibits protein synthesis through an interaction with elongation factor Tu, against a wide range of recent clinical isolates of common aerobic gram-positive and anaerobic organisms was determined. MDL 62,879 was highly active against staphylococci (MIC for 90% of isolates [MIC_{90}], 0.125 μg/ml), streptococci (MIC_{90}, 1 μg/ml), and enterococci (MIC_{90}, 0.03 μg/ml). All isolates of peptostreptococci and *Mobiluncus* spp. were susceptible, as were most isolates of clostridia. MDL 62,879 was not active against isolates of fusobacteria or *Bacteroides* spp., but some isolates of *Prevotella* spp. and *Porphyromonas asaccharolytica* were susceptible.

The numbers of infections with gram-positive organisms, particularly infections with coagulase-negative staphylococci associated with intravascular catheters, are increasing (1, 6). These organisms are often resistant to the agents most frequently used for the treatment of gram-positive infections (4). Recent reports of glycopeptide resistance in coagulase-negative staphylococci and enterococci (3) increase the need for the development of agents active against these multiple-drug-resistant organisms. A recent report of a new agent, MDL 62,879 (GE2270 A), which inhibits protein synthesis by interacting with protein synthesis elongation factor Tu, suggested that this agent was active against gram-positive bacteria (5). We report on the in vitro activity of MDL 62,879 against a wide range of aerobic gram-positive and anaerobic organisms.

MATERIALS AND METHODS

Organisms. The strains included in the study were all clinical isolates selected to include representative numbers of different species, some of which were known to be resistant to the other agents tested. Three isolates of *Enterococcus faecium* resistant to vancomycin were supplied by G. French, Department of Microbiology, United Medical and Dental Schools, Guys Campus, while all the remaining organisms were isolated at St. Thomas' Hospital. Isolates were identified by routine laboratory methods, coagulase-negative staphylococci by use of the API ID 32 Staph system and nongroupable streptococci and enterococci by use of the API 20 Strep system. Anaerobic bacteria were identified by use of the API 20A system and gas-liquid chromatography.

Antimicrobial agents. The agents tested were gifts from the manufacturers. MDL 62,879 (Lepetit) was supplied as a solution containing 9.4 mg of drug per ml; other agents, supplied as powders of known potency, were teicoplanin and rifampin (Lepetit), penicillin and methicillin (SmithKline Beecham), erythromycin (Abbott Laboratories), clindamycin (Upjohn), vancomycin (Eli Lilly), cefoxitin (Merck Sharp & Dohme), and metronidazole (Rhone-Poulenc).

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MIC determinations. An agar dilution method was used, and plates were inoculated with a 36-pin multipoint inoculator (Denley). The medium for aerobic bacteria, including methicillin-resistant staphylococci, was diagnostic sensitivity test agar (Oxoid CM261) supplemented with 5% lysed horse blood for fastidious streptococci; that for anaerobic bacteria was Wilkins-Chalgren agar (Oxoid CM619) supplemented with 5% saponin-lysed horse blood. The bacteria were either grown in brain heart infusion broth (Oxoid CM266) or suspended in broth from fresh agar cultures and diluted to yield a final inoculum of 5×10^4 CFU per spot. Aerobic bacteria were incubated overnight at 37°C in air (CO_2 for alpha-hemolytic streptococci), and anaerobic bacteria were incubated at 37°C for 48 h in N_2-CO_2-H_2 (80:10:10). *Staphylococcus aureus* NCTC 6571 was included as a control for all aerobic tests, and *Bacteroides fragilis* NCTC 9343 was included as a control for anaerobic tests. The MIC of MDL 62,879 for *S. aureus* was 0.06 μg/ml, and that for *B. fragilis* was >64 μg/ml. The MICs of the other agents for the controls were as listed in the working party recommendations for the British Society for Antimicrobial Chemotherapy (7).

RESULTS

The MICs of the agents tested against aerobic gram-positive bacteria are listed in Table 1. All staphylococci were susceptible to <1 μg of MDL 62,879 per ml, including those resistant to penicillin, methicillin, erythromycin, or clindamycin. Both alpha- and beta-hemolytic streptococci were slightly less susceptible than staphylococci, but all isolates were inhibited by <4 μg of MDL 62,879 per ml, including those resistant to the other agents tested. MDL 62,879 was the most active of the agents tested against enterococci. All isolates of *E. faecalis*, including six isolates highly resistant to the aminoglycosides, were inhibited by 0.03 μg/ml, as were both vancomycin-susceptible and vancomycin-resistant isolates of *E. faecium*. MDL 62,879 was more active against enterococci than against staphylococci or streptococci.

MDL 62,879 was active against many anaerobic bacteria (Table 2). All peptostreptococci were susceptible, and there

TABLE 1. In vitro activity against aerobic gram-positive bacteria

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
S. aureus, methicillin susceptible (31)	MDL 62,879	0.03–0.06	0.06	0.06
	Penicillin	0.016–32	0.125	8
	Erythromycin	0.06–>128	0.125	8
	Clindamycin	0.03–0.25	0.125	0.125
	Vancomycin	1–2	1	1
	Teicoplanin	0.25–2	0.5	1
	Rifampin	0.001–2	0.008	0.016
S. aureus, methicillin resistant (9)	MDL 62,879	0.03–0.06	0.03	0.06
	Penicillin	8–32	8	32
	Erythromycin	0.125–>128	4	>128
	Clindamycin	0.06–0.125	0.06	0.125
	Vancomycin	1–2	1	2
	Teicoplanin	0.25–2	1	2
	Rifampin	0.002–2	0.008	2
Coagulase-negative staphylococci, methicillin susceptible (29)[b]	MDL 62,879	0.03–0.25	0.06	0.125
	Penicillin	0.016–32	0.25	4
	Erythromycin	0.125–>32	0.25	>32
	Clindamycin	0.06–>32	0.06	0.25
	Vancomycin	0.5–2	2	2
	Teicoplanin	0.125–4	1	2
	Rifampin	0.001–0.03	0.016	0.03
Coagulase-negative staphylococci, methicillin resistant (11)[c]	MDL 62,879	0.03–0.25	0.125	0.125
	Penicillin	0.06–128	4	128
	Erythromycin	0.25–>32	4	>32
	Clindamycin	0.03–0.25	0.125	0.25
	Vancomycin	1–2	2	2
	Teicoplanin	1–4	2	4
	Rifampin	0.008–0.03	0.016	0.03
S. saprophyticus (20)	MDL 62,879	0.06–0.5	0.125	0.25
	Penicillin	0.06–0.25	0.25	0.25
	Methicillin	0.5–8	8	8
	Erythromycin	0.06–0.25	0.125	0.25
	Clindamycin	0.06–0.5	0.125	0.125
	Vancomycin	1–2	2	2
	Teicoplanin	0.5–4	2	2
	Rifampin	0.008–0.06	0.03	0.06
Beta-hemolytic streptococci, groups A, C, and G (40)	MDL 62,879	0.125–0.5	0.5	0.5
	Penicillin	0.002–0.008	0.008	0.008
	Erythromycin	0.008–2	0.03	0.06
	Clindamycin	0.008–0.125	0.03	0.06
	Vancomycin	0.5		
	Teicoplanin	0.03–0.25	0.125	0.25
	Rifampin	0.016–0.25	0.06	0.125
Streptococcus agalactiae (25)	MDL 62,879	0.25–2	1	1
	Penicillin	0.008–0.03	0.03	0.03
	Erythromycin	0.016–0.03	0.03	0.03
	Clindamycin	0.03–0.06	0.06	0.06
	Vancomycin	0.5–1	0.5	1
	Teicoplanin	0.03–0.06	0.06	0.06
	Rifampin	0.03–128	0.125	1

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TABLE 1—*Continued*

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
S. pneumoniae (20)	MDL 62,879	0.125–0.5	0.25	0.25
	Penicillin	0.008–2	0.016	0.25
	Erythromycin	0.06–>32	0.06	0.125
	Clindamycin	0.06–>32	0.125	0.125
	Vancomycin	0.25–0.5	0.5	0.5
	Teicoplanin	0.016–0.125	0.06	0.125
	Rifampin	0.016–32	0.03	0.06
Other alpha-hemolytic streptococci (19)	MDL 62,879	0.06–1	0.5	1
	Penicillin	0.008–0.25	0.03	0.125
	Erythromycin	0.016–0.125	0.03	0.06
	Clindamycin	0.008–0.125	0.03	0.06
	Vancomycin	0.5–1	1	1
	Teicoplanin	0.016–0.5	0.06	0.5
	Rifampin	0.016–0.25	0.06	0.125
E. faecalis (22)	MDL 62,879	0.008–0.03	0.03	0.03
	Ampicillin	0.5–2	1	1
	Erythromycin	0.25–>128	1	2
	Clindamycin	0.5–>128	8	16
	Vancomycin	0.5–8	1	2
	Teicoplanin	0.06–0.25	0.12	0.25
	Rifampin	0.25–16	1	2
E. faecium, vancomycin susceptible (5)	MDL 62,879	0.004–0.03		
	Ampicillin	32–32		
	Erythromycin	1–>128		
	Clindamycin	0.06–8		
	Teicoplanin	0.25–0.5		
	Rifampin	0.06–2		
E. faecium, vancomycin resistant (3)	MDL 62,879	0.03–0.03		
	Ampicillin	128–>128		
	Erythromycin	>128		
	Clindamycin	0.25–>128		
	Teicoplanin	32–>128		
	Rifampin	2–8		

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[b] Nineteen *S. epidermidis*, 3 *S. haemolyticus*, 3 *S. hominis*, 2 *S. simulans*, and 1 each of *S. warneri* and a *Micrococcus* sp.
[c] Seven *S. epidermidis*, two *S. haemolyticus*, and one each of *S. cohnii* and *S. xylosus*.

was little difference between the different species, although isolates of *Peptostreptococcus asaccharolyticus* tended to be the most susceptible. Clostridia were susceptible, with the exception of one isolate of *Clostridium clostridiiforme*. MDL 62,879 was also active against some gram-negative anaerobic bacteria. All isolates of *Mobiluncus* spp. were highly susceptible, as were most *Porphyromonas asaccharolytica* isolates and most isolates of *Prevotella* spp., with the exception of *Prevotella oris/buccae*, of which only 3 of 10 isolates were susceptible. Most *Bacteroides* spp. were resistant to MDL 62,879, except for *B. uniformis*, of which all but two isolates were susceptible. Most isolates of *B. fragilis* and *B. distasonis* were partially or totally inhibited in the range of 2 to 8 μg/ml but grew at higher concentrations, resulting in higher MICs, of >64 μg/ml. Fusobacteria were also resistant. There was no evidence of cross-resistance with the other agents tested.

DISCUSSION

Our results for MDL 62,879 are similar to those of other workers for aerobic gram-positive species (2). MDL 62,879 had excellent activity against all the gram-positive species tested, both aerobic and anaerobic, with only 1 resistant isolate, *C. clostridiiforme*, among the 291 gram-positive isolates included in this study. The susceptible isolates included *C. difficile*, which is often resistant to antimicrobial agents with anaerobic activity. Perhaps the most striking feature was the activity of MDL 62,879 against enterococci, which are usually the aerobic species least susceptible to other agents with gram-positive aerobic activity, including isolates resistant to vancomycin and teicoplanin and isolates highly resistant to β-lactams and aminoglycosides. MDL 62,879 had no useful activity against *Bacteroides* spp. or fusobacteria, but significant numbers of other gram-negative anaerobes were susceptible. We are unable at present to explain the inhibition of growth of *B. fragilis* and *B. distasonis* by intermediate concentrations but not higher concentrations of the antibiotic.

MDL 62,879 is novel in both structure and mode of action, although in the latter it resembles the kirromycins, which are not used in humans, so it is not surprising that there was no cross-resistance with the other agents tested. The development of this new agent, to which there is virtually no in vitro

TABLE 2. In vitro activity against anaerobic bacteria

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
Peptostreptococcus spp. (38)[b]	MDL 62,879	0.001–0.03	0.016	0.03
	Metronidazole	0.06–1	0.25	1
	Cefoxitin	0.03–16	0.5	8
	Clindamycin	0.002–0.25	0.06	0.125
Clostridium spp. (24)[c]	MDL 62,879	0.016–>64	0.06	2
	Metronidazole	0.016–1	0.25	0.5
	Cefoxitin	0.5–64	8	32
	Clindamycin	0.016–>128	1	4
Mobiluncus spp. (20)[d]	MDL 62,879	0.001–0.03	0.001	0.016
	Metronidazole	4–>128	128	>128
	Cefoxitin	0.125–1	0.5	1
	Clindamycin	0.008–0.03	0.016	0.03
Prevotella spp. (57)[e]	MDL 62,879	0.004–>64	1	>64
	Metronidazole	0.03–1	0.5	1
	Cefoxitin	0.06–16	1	4
	Clindamycin	0.002–0.25	0.008	0.016
P. asaccharolytica (7)	MDL 62,879	0.03–>64		
	Metronidazole	0.06–0.125		
	Cefoxitin	0.03–2		
	Clindamycin	0.001–0.008		
Bacteroides spp. (70)[f]	MDL 62,879	0.5–>64	>64	>64
	Metronidazole	0.125–2	1	2
	Cefoxitin	0.125–>128	0.5	4
	Clindamycin	0.008–>128	4	8
Fusobacterium spp. (18)[g]	MDL 62,879	2–>64	>64	>64
	Metronidazole	0.008–0.25	0.016	0.25
	Cefoxitin	0.06–1	0.25	1
	Clindamycin	0.016–0.06	0.03	0.06

[a] See Table 1, footnote *a*.
[b] Sixteen *P. anaerobius*, 7 *P. asaccharolyticus*, 7 *P. magnus*, 3 *P. micros*, and 5 *P. prevotii*.
[c] Four *C. butyricum*, five *C. clostridiiforme*, four *C. difficile*, six *C. perfringens*, and five *C. ramosum*.
[d] Twelve *M. curtisii* and 8 *M. mulieris*.
[e] Ten *P. bivia*, 10 *P. disiens*, 10 *P. intermedia*, 7 *P. melaninogenica*, 10 *P. oralis*, and 10 *P. oris/buccae*.
[f] Ten each of *B. distasonis*, *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, and *B. ureolyticus*.
[g] Ten *F. necrophorum* and 8 *F. nucleatum*.

resistance in gram-positive species, is opportune, and we believe that it deserves clinical investigation. Special attention will have to be paid to the emergence of resistance, which is reported to occur, albeit rarely, in vitro (2).

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