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Activity of Mersacidin, a Novel Peptide, Compared with That of Vancomycin, Teicoplanin, and Daptomycin

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Mersacidin, a new peptide antibiotic, was four- to eightfold less active (MIC for 90% of isolates, 8 μg/ml) than vancomycin, teicoplanin, or daptomycin against *Staphylococcus aureus*. Coagulase-negative staphylococci were inhibited by 8 μg/ml, and the MICs of mersacidin for hemolytic streptococci and *Streptococcus pneumoniae* were 4 to 8 μg/ml. The mersacidin MICs for anaerobic organisms were as follows: *Clostridium perfringens*, 4 μg/ml; *Propionibacterium acnes*, 8 μg/ml; peptococci, 1 μg/ml; and peptostreptococci, 8 μg/ml. Mersacidin had no activity against members of the family *Enterobacteriaceae*, *Neisseria* and *Haemophilus* species, or *Pseudomonas aeruginosa*. The size of the inoculum, the pH of the assay (5.5 to 7.5), the type of medium, and the anaerobic conditions had minimal effects on the MICs and MBCs of mersacidin. Overall, mersacidin proved less active than available glycopeptides and peptolides.

The increasing importance of gram-positive bacteria in hospital infections has caused a renewed investigation of compounds with activity against staphylococci and enterococci (1, 2, 4). Methicillin-resistant *Staphylococcus aureus* is a serious problem in hospitals in many countries, and the only effective antibacterial agents have been glycopeptides, vancomycin, and teicoplanin. Mersacidin is a novel peptide recently isolated from a *Bacillus* species (3). We wished to determine the in vitro activity of mersacidin and to compare its activity with that of glycopeptides and with that of a peptolide, daptomycin.

Mersacidin was a gift from William Novick of Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. Vancomycin and daptomycin were provided by Lilly Research Laboratories, Indianapolis, Ind., and teicoplanin was provided by Merrell Dow Pharmaceuticals, Inc., Cincinnati, Ohio.

Bacterial strains were obtained from patients hospitalized at the Columbia-Presbyterian Medical Center in New York City and included isolates retained over the past year because of known resistance to β-lactams, quinolones, and aminoglycosides.

Antimicrobial activity was measured by an agar dilution method with Mueller-Hinton agar, unless otherwise specified (5). A final inoculum of 10^4 CFU for aerobic species and 10^5 CFU for anaerobic species was applied with a replicating device. Broth dilution tests were performed with 5×10^5 CFU in 1-ml tubes. Cultures of test organisms were grown overnight in Mueller-Hinton broth (BBL Microbiology Systems, Cockeysville, Md.), Schaedler broth (*Haemophilus*, *Branhamella*, and *Neisseria* spp.), and chopped-meat glucose (Scott Laboratories, Inc., Providence, R.I.) (anaerobic species). The susceptibility of *Haemophilus* spp. was determined with chocolate Mueller-Hinton agar in the presence of 5% CO_2. The susceptibilities of streptococci were determined with Mueller-Hinton agar supplemented with 5% sheep blood, and the susceptibilities of anaerobic species were determined with brucella agar supplemented with sheep blood, hemin, and vitamin K. Aerobic cultures were incubated at 35°C for 18 h, and anaerobic cultures were incubated for 48 h in GasPak jars (BBL). The susceptibilities of methicillin-resistant staphylococci were determined with Mueller-Hinton agar supplemented with 3% NaCl; isolates for which oxacillin MICs were >8 μg/ml were considered resistant. The MIC was defined as the lowest concentration of antibiotic that inhibited the development of visible growth on agar or in broth. MBCs were determined by removing 0.01-ml samples from clear 1-ml tubes and plating them on an antibiotic-free medium. The MBC was the concentration that resulted in a 99.9% reduction in CFU compared with the original culture according to the method of Pearson et al. (6). All tests were run with American Type Culture Collection control strains of *S. aureus* and *Enterococcus faecalis*.

The activity of mersacidin is shown in Table 1. In general, mersacidin was four- to eightfold less active than vancomycin, teicoplanin, and daptomycin against staphylococci. This was particularly true for the methicillin-resistant isolates, for some of which the MICs were 32 μg/ml. The mersacidin MIC for 90% of the *S. aureus* and *Staphylococcus epidermidis* isolates was 8 μg/ml. Mersacidin was less active than the comparative agents against the hemolytic streptococci. Although 90% of *Streptococcus pyogenes* isolates were inhibited by 2 μg of mersacidin per ml, 8 μg/ml was required to inhibit 90% of group B, C, and G streptococci, whereas 0.5 to 1 μg of the other agents per ml inhibited these species. Mersacidin had particularly poor activity against *E. faecalis* (MIC, 64 μg/ml) and viridans group streptococci, including *Streptococcus mutans* and *Streptococcus sanguis* (MICs, 4 to 32 μg/ml). *Listeria monocytogenes* was poorly inhibited (MICs, 16 to 32 μg/ml), whereas *Corynebacterium jeikeium* was inhibited by 4 μg/ml, as were 90% of *Clostridium perfringens* isolates. Other *Clostridium* species, such as *C. difficile* and *C. septicum*, were inhibited by 4 to 8 μg/ml, as were peptostreptococci and peptococci.

Mersacidin did not inhibit (MIC, >128 μg/ml; 10 isolates each) *Bacteroides fragilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. The effects of various growth conditions on

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TABLE 1. In vitro activities of mersacidin and other agents

Organism (no. tested)	Agent	MIC (μg/ml)[a]		
		Range	50%	90%
Staphylococcus aureus, methicillin susceptible (32)	Mersacidin	2–16	4	8
	Vancomycin	0.5–2	1	1
	Teicoplanin	0.25–2	0.5	1
	Daptomycin	0.25–0.5	0.5	0.5
Staphylococcus aureus, methicillin resistant (44)	Mersacidin	1–32	4	16
	Vancomycin	0.5–2	1	2
	Teicoplanin	0.25–2	1	2
	Daptomycin	0.12–1	0.5	1
Staphylococcus epidermidis, methicillin susceptible (30)	Mersacidin	0.5–16	4	8
	Vancomycin	0.25–1	1	1
	Teicoplanin	0.25–8	1	2
	Daptomycin	0.03–0.5	0.25	0.5
Staphylococcus epidermidis, methicillin resistant (45)	Mersacidin	0.5–16	4	8
	Vancomycin	0.25–2	1	2
	Teicoplanin	0.25–8	2	4
	Daptomycin	0.12–0.5	0.25	0.5
Streptococcus pyogenes (20)	Mersacidin	0.5–8	1	2
	Vancomycin	0.25–1	0.25	1
	Teicoplanin	0.03–0.5	0.12	0.12
	Daptomycin	0.06–0.5	0.25	0.5
Streptococcus agalactiae (23)	Mersacidin	1–8	8	8
	Vancomycin	0.25–1	0.5	1
	Teicoplanin	0.12–0.25	0.25	0.25
	Daptomycin	0.12–0.5	0.25	0.5
Group C streptococci (20)	Mersacidin	2–8	4	8
	Vancomycin	0.25–1	0.5	1
	Teicoplanin	0.03–0.25	0.25	0.25
	Daptomycin	0.06–4	0.25	4
Group G streptococci (18)	Mersacidin	2–8	8	8
	Vancomycin	0.25–1	0.5	0.5
	Teicoplanin	0.06–0.25	0.12	0.25
	Daptomycin	0.06–2	0.25	2
Streptococcus bovis (10)	Mersacidin	4–8	4	8
	Vancomycin	0.25–0.5	1	0.5
	Teicoplanin	0.06–0.5	0.12	0.25
	Daptomycin	0.12–4	0.25	0.5
Viridans group streptococci (20)	Mersacidin	0.5–32	4	32
	Vancomycin	0.25–1	0.5	1
	Teicoplanin	0.03–128	0.06	128
	Daptomycin	0.25–4	1	2
Enterococcus faecalis (40)	Mersacidin	64	64	64
	Vancomycin	1–4	2	4
	Teicoplanin	0.25–1	0.5	1
	Daptomycin	0.5–4	2	4
Streptococcus pneumoniae (23)	Mersacidin	1–4	2	4
	Vancomycin	0.12–0.5	0.25	0.5
	Teicoplanin	0.06–0.5	0.12	0.25
	Daptomycin	0.03–2	0.06	0.5
Corynebacterium jeikeium (18)	Mersacidin	2–4	4	4
	Vancomycin	0.25–0.5	0.5	0.5
	Teicoplanin	0.25–1	0.5	0.5
	Daptomycin	0.06–0.25	0.12	0.12
Listeria monocytogenes (20)	Mersacidin	16–64	16	32
	Vancomycin	1–4	1	2
	Teicoplanin	0.06–0.5	0.25	0.5
	Daptomycin	2–4	4	4
Clostridium perfringens (15)	Mersacidin	0.5–8	2	4
	Vancomycin	0.25–0.5	0.5	0.5
	Teicoplanin	0.06–2	0.25	0.5
	Daptomycin	4–16	4	8
Clostridium spp.[b] (18)	Mersacidin	1–16	4	8
	Vancomycin	0.25–1	0.5	1
	Teicoplanin	0.03–1	0.03	0.25
	Daptomycin	2–16	8	16
Peptostreptococci (17)	Mersacidin	0.5–8	2	8
	Vancomycin	0.5–8	2	8
	Teicoplanin	0.12–1	0.12	0.5
	Daptomycin	0.12–4	1	2
Propionibacterium acnes (13)	Mersacidin	1–16	8	8
	Vancomycin	0.12–1	0.25	0.5
	Teicoplanin	0.12–1	0.25	0.5
	Daptomycin	0.5–32	4	16

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[b] Includes *C. ramosum* (n = 5), *C. novyi* (n = 5), *C. septicum* (n = 3), and *C. difficile* (n = 5).

the activity of mersacidin were determined. Against 30 staphylococci, mersacidin was equally active at pH 5.5, 6.5, and 7.5. An inoculum of 10^7 CFU compared with an inoculum of 10^5 CFU did not increase the MICs for methicillin-susceptible and methicillin-resistant *S. aureus* (eight isolates each). The MICs of mersacidin were within a dilution (error of the method) for staphylococci with Mueller-Hinton medium, Mueller-Hinton medium supplemented with 3% NaCl, brain heart infusion agar, and nutrient agar. The activity of mersacidin against *S. aureus* (methicillin susceptible and methicillin resistant) was similar under aerobic and anaerobic conditions. The addition of 5% sheep blood to agar did not alter the MICs for *S. aureus*, *S. epidermidis*, or *E. faecalis*. Mersacidin was bactericidal for staphylococci and streptococci, with MBCs within twofold of the MICs. However, there was an 8- to 16-fold difference in MBCs and MICs for *E. faecalis* and *Enterococcus faecium*.

Overall, mersacidin is appreciably less active than are the glycopeptides, vancomycin, and teicoplanin. It does inhibit methicillin-resistant *S. aureus* and organisms such as *Corynebacterium jeikeium*. Ganguli et al. (3) reported that mersacidin was more effective in a mouse model of septicemia than was vancomycin, which was fourfold more active in vitro. Further investigation of this compound or possible chemical modification or both may yield an agent that can be used against problem gram-positive species.

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