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Comparative In Vitro Activities of Teicoplanin, Daptomycin, Ramoplanin, Vancomycin, and PD127,391 against Blood Isolates of Gram-Positive Cocci

DOKUN SHONEKAN,* DONNA MILDVAN, AND SANDRA HANDWERGER

Division of Infectious Diseases, Department of Medicine, Beth Israel Medical Center, New York, New York 10003

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The in vitro activities of teicoplanin, daptomycin, ramoplanin, and PD127,391, a new quinolone, were compared with that of vancomycin. Teicoplanin showed the lowest MICs against *Enterococcus faecalis*. Ramoplanin was slightly more active than the other peptide antibiotics against oxacillin-resistant *Staphylococcus aureus*. The MICs of the four peptide antibiotics were similar for the oxacillin-susceptible *S. aureus*. Daptomycin had good activity against staphylococci but was the least active agent against *E. faecalis*. The MICs of vancomycin against all isolates were in general higher than those of the new antibiotics, with the exceptions of the MICs of daptomycin against *E. faecalis* and teicoplanin against oxacillin-resistant *Staphylococcus epidermidis*. PD127,391 was the most active agent against all staphylococcal isolates.

Some new antibiotics have been reported to show good activity against gram-positive bacteria. Four of these, teicoplanin, daptomycin, ramoplanin, and PD127,391, are compared with vancomycin in the present study. The glycopeptide antibiotics teicoplanin and vancomycin inhibit peptidoglycan synthesis (14, 18). Daptomycin, a lipopeptide, appears to inhibit the synthesis of peptidoglycan precursors by disruption of the transmembrane potential (1). The lipoglycopeptide antibiotic ramoplanin inhibits the formation of lipid intermediate II from lipid intermediate I, a later step in peptidoglycan synthesis (21). PD127,391 is a quinolone which has an in vitro potency significantly higher than that of ciprofloxacin (10, 16).

In recent years, as the use of vancomycin has become more widespread, resistance has emerged among coagulase-negative staphylococci and enterococci (5, 9, 20, 23). Schwalbe et al. (19) demonstrated emergence of vancomycin resistance in *Staphylococcus haemolyticus* isolated from a patient being treated continuously with vancomycin. The possibility of development of vancomycin resistance among methicillin-resistant *Staphylococcus aureus* cannot be discounted. Glycopeptide resistance, often mediated by conjugative plasmids, is being recognized with increasing frequency among enterococci (7, 11, 20). In addition to the emergence of resistance, the cost and toxicity of vancomycin make it important for investigators to look for alternative therapy.

In the present study, susceptibility testing was performed upon 130 strains obtained from blood cultures of patients at Beth Israel Medical Center. Strains were stored at −70°C in Mueller-Hinton broth with 15% glycerol and were subcultured in appropriate media prior to antimicrobial susceptibility testing. The antibiotics tested were daptomycin and vancomycin (both from Eli Lilly & Co., Indianapolis, Ind.), teicoplanin and ramoplanin (both from Marion Merrell Dow Research Institute, Cincinnati, Ohio), and PD127,391 (Warner-Lambert Co., Ann Arbor, Mich). MICs were determined by the standard microdilution broth technique recommended by the National Committee for Clinical Laboratory Standards (15), in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with 25 mg of $MgCl_2$ and 50 mg of $CaCl_2$ per liter. *S. aureus* 29213 and *Enterococcus faecalis* 29212 were used as control organisms.

Results are summarized in Table 1. Teicoplanin had the lowest MICs against *E. faecalis* for 50 and 90% of strains tested (0.125 and 0.5 μg/ml, respectively). Although all enterococcal isolates tested were susceptible to the five agents, daptomycin was the least active.

PD127,391 was the most active agent against all staphylococcal isolates. It was five- to sixfold more active than the glycopeptide antibiotics for oxacillin-susceptible staphylococci and slightly more active than the glycopeptide antibiotics for oxacillin-resistant staphylococci. The five antibiotics tested displayed comparable activities against oxacillin-resistant *S. aureus*, though ramoplanin had slightly lower MICs and vancomycin had slightly higher MICs for 50% of the isolates than the other three peptide antibiotics. The activities of the four peptide antibiotics were similar for oxacillin-susceptible *S. aureus*.

All of the antimicrobial agents tested were active against oxacillin-susceptible *Staphylococcus epidermidis*. The 25 oxacillin-resistant strains of *S. epidermidis* were susceptible to daptomycin, ramoplanin, vancomycin, and PD127,391, with MICs for 90% of the strains at 0.5, 0.5, 2, and 0.25 μg/ml, respectively. Teicoplanin was slightly more active than vancomycin against staphylococcal isolates, with the exception of oxacillin-resistant *S. epidermidis*. These isolates showed a wide range of MICs, from 0.25 to 16 μg/ml. At the 8- and 32-μg/ml breakpoint levels of the National Committee for Clinical Laboratory Standards (8), 22 of the oxacillin-resistant *S. epidermidis* isolates were susceptible to teicoplanin, and 3 of 25 (12%) were intermediately susceptible to teicoplanin, with MICs of 16 μg/ml. These MICs for oxacillin-resistant *S. epidermidis* were higher than those found by some previous investigators (2, 6, 17). However, Goldstein et al. (5) reported that *S. epidermidis* represented 74% of the teicoplanin-resistant coagulase-negative staphylococci. According to these breakpoint levels, there were no resistant isolates among tested strains from this hospital.

* Corresponding author.

TABLE 1. MICs of teicoplanin, daptomycin, ramoplanin, vancomycin, and PD127,391 against gram-positive blood culture isolates

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)[a]		
		50%	90%	Range
Enterococcus faecalis (30)	Teicoplanin	0.125	0.5	≤0.06–0.5
	Daptomycin	2	4	1.0–8
	Ramoplanin	0.5	0.5	0.25–1
	Vancomycin	1	2	0.5–2
	PD127,391	0.25	1	0.12–4
Staphylococcus aureus				
Oxacillin-resistant (35)	Teicoplanin	0.5	1	0.25–2
	Daptomycin	0.25	1	0.25–2
	Ramoplanin	0.25	0.5	0.125–0.5
	Vancomycin	1	1	0.5–2
	PD127,391	0.06	0.5	0.03–1
Oxacillin-susceptible (20)	Teicoplanin	0.25	0.5	0.25–0.5
	Daptomycin	0.25	0.5	0.25–0.5
	Ramoplanin	0.25	0.5	0.25–1
	Vancomycin	0.5	1	0.5–1
	PD127,391	0.03	0.03	0.015–0.03
Staphylococcus epidermidis				
Oxacillin-resistant (25)	Teicoplanin	4	8	0.25–16
	Daptomycin	0.25	0.5	0.25–0.5
	Ramoplanin	0.125	0.5	0.125–0.5
	Vancomycin	2	2	1–2
	PD127,391	0.03	0.25	0.015–2
Oxacillin-susceptible (20)	Teicoplanin	0.25	2	≤0.06–4
	Daptomycin	0.25	0.5	≤0.06–0.5
	Ramoplanin	0.25	0.25	≤0.06–0.25
	Vancomycin	0.5	1	0.5–2
	PD127,391	0.03	0.06	0.03–0.06

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

If teicoplanin is found to be less toxic and easier to administer than vancomycin, as already reported (22), this agent may have a therapeutic advantage.

Daptomycin-resistant mutants can be selected in vitro among pneumococci, enterococci, and coagulase-positive and -negative staphylococci. The frequency was found to be highest with pneumococci and lowest with *S. aureus* (12). The development of resistance in the clinical setting has not yet been determined. Daptomycin, like the other new peptide antibiotics, shows better in vitro activity than does vancomycin against oxacillin-susceptible and -resistant *S. aureus* but was less active than vancomycin and the other antibiotics against enterococci. The original clinical trials with daptomycin were suspended because of treatment failures in patients with infections caused by gram-positive cocci (3). A more recent study by Garrison et al. (4) suggests that clinical failures may be due to the high level of protein binding associated with daptomycin and that larger daily doses might be more successful in treating infections caused by gram-positive cocci. Daptomycin is undergoing further clinical evaluation with a higher-dosage regimen.

In our study, ramoplanin had better activity against enterococci than did vancomycin, daptomycin, or PD127,391. It also was reported to have better bactericidal activity than teicoplanin and vancomycin against methicillin- and gentamicin-resistant *S. aureus* (13). Clinical studies of ramoplanin may be warranted.

PD127,391 showed good activity against all isolates. Previous in vitro studies indicated that it has excellent activity against both gram-positive and -negative bacterial species, including *Chlamydia* spp. and *Mycobacterium tuberculosis*. It was found to be two- to eight-fold more active than ciprofloxacin (10, 16, 24). Our data on the gram-positive cocci tested support previously reported susceptibility findings for this agent. The results indicate that further in vitro and in vivo studies of this quinolone are justified.

In conclusion, the results of this study demonstrate the good potential of teicoplanin, daptomycin, ramoplanin, and PD127,391 as therapeutic agents for infections caused by gram-positive cocci.

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