ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1989, p. 2019–2022
0066-4804/89/112019-04$02.00/0

Vol. 33, No. 11

Comparative In Vitro Activities of Teicoplanin, Vancomycin, Oxacillin, and Other Antimicrobial Agents against Bacteremic Isolates of Gram-Positive Cocci

EUGENE A. GORZYNSKI,[1,2]* DANIEL AMSTERDAM,[2,3,4] THOMAS R. BEAM, JR.,[1,2,4] AND COLEMAN ROTSTEIN[4,5]†

Veterans Administration Medical Center[1] and Erie County Medical Center,[3] Buffalo, New York 14215; Roswell Park Memorial Institute, Buffalo, New York 14263[5]; and Departments of Medicine[4] and Microbiology,[2] State University of New York at Buffalo, Buffalo, New York 14214

Received 19 June 1989/Accepted 24 August 1989

The in vitro activities of teicoplanin and vancomycin were compared with those of six other antimicrobial agents against 460 bacteremic isolates of gram-positive cocci. Teicoplanin was as active as vancomycin but less active than ciprofloxacin against staphylococci. Teicoplanin was the most potent of all agents tested against enterococci and had excellent activity against pneumococci.

Teicoplanin and vancomycin are glycopeptide antimicrobial agents possessing similar activities against most gram-positive cocci at concentrations of <1 μg/ml (11). We compared the in vitro activity of teicoplanin with those of vancomycin, penicillin, gentamicin, clindamycin, trimethoprim-sulfamethoxazole, and ciprofloxacin against 460 oxacillin-resistant and oxacillin-susceptible clinical isolates of staphylococci, enterococci, and *Streptococcus pneumoniae*.

(This work was presented in part at the 88th Annual Meeting of the American Society for Microbiology, Miami Beach, Fla., 8 to 13 May 1988.)

All strains were obtained from blood cultures of patients at three teaching hospitals in Buffalo, N.Y.: Veterans Administration Medical Center, Erie County Medical Center, and Roswell Park Memorial Institute. The microorganisms were detected by the BACTEC 460 (Johnston Laboratories, Inc., Towson, Md.) (former two hospitals) or the Septi-Chek (Roche Diagnostics, Div. Hoffmann-La Roche Inc., Nutley, N.J.) (latter hospital). After initial recovery on 5% sheep blood agar, isolates were preliminarily identified in participating laboratories. Subcultures on blood agar were transported to the Veterans Administration Medical Center for final identification, storage of accessioned strains, and determination of antimicrobial susceptibility to test agents. *Staphylococcus aureus* was confirmed by slide hemagglutination (Staphyloslide; BBL Microbiology Systems, Cockeysville, Md.); coagulase-negative staphylococci were identified to the species level by the Staph-Ident system (Analytab Products, Plainview, N.Y.). Enterococci were identified by growth in bile esculin and in 6.5% NaCl. *S. pneumoniae* was characterized by bile solubility and optochin susceptibility. All strains were stored at −70°C in brain heart infusion broth with 10% glycerol until thawed at room temperature and subcultured prior to antimicrobial susceptibility testing.

Antimicrobial reference powders were obtained as follows: teicoplanin (Merrell Dow Research Institute, Cincinnati, Ohio), vancomycin (Lilly Research Laboratories, Indianapolis, Ind.), penicillin (Wyeth Laboratories, Inc., West Chester, Pa.), gentamicin (Schering-Plough Corp., Kenilworth, N.J.), clindamycin (The Upjohn Co., Kalamazoo, Mich.), trimethoprim-sulfamethoxazole (Burroughs Wellcome Co., Research Triangle Park, N.C.), ciprofloxacin (Miles Pharmaceuticals, West Haven, Conn.), and oxacillin (Bristol-Myers Co., Evansville, Ind.).

Antimicrobial susceptibility was determined by a broth microdilution technique recommended by the National Committee for Clinical Laboratory Standards (10). The reagent powders were dissolved in accordance with manufacturer instructions, diluted in Mueller-Hinton broth supplemented with 2% sodium chloride, and distributed (0.1 ml) to wells in microdilution trays. The trays were stored at −70°C until thawed at room temperature immediately before use. After inoculation to yield about 5×10^4 CFU per well, the trays were incubated at 35°C for 24 h. MICs of all antimicrobial agents were recorded as the lowest concentrations that completely inhibited visible growth of the test strain. Data were analyzed by a customized computer program (MICom; AMData Resources, Amherst, N.Y.). Antimicrobial concentrations that inhibited 50 and 90% of the strains and percentages resistant were calculated in accordance with National Committee for Clinical Laboratory Standards interpretive breakpoints (10). Enterococcal strains resistant to >64 μg of gentamicin per ml were tested further with high-content (2,000-μg) gentamicin disks as described by Rosenthal and Freundlich (12) and as modified by Sahm and Torres (13). Briefly, sufficient gentamicin in 0.025 ml of water was applied to sterile blank disks (diameter, 6 mm; Difco Laboratories, Detroit, Mich.) to yield 2,000 μg per disk. Disks were air dried and stored at 4°C in sterile petri dishes until used. An enterococcal strain with ≤12 mm of inhibition around a 2,000-μg gentamicin disk was characterized as synergy resistant (12, 13).

Activities of teicoplanin, vancomycin, and other antimicrobial agents against oxacillin-susceptible and oxacillin-resistant strains were compared (Table 1). For teicoplanin and vancomycin, ≥32 μg/ml was used as the standard interpretive breakpoint of resistance. Of all the agents tested against *S. aureus*, teicoplanin, vancomycin, trimethoprim-sulfamethoxazole, and ciprofloxacin were the most active against both oxacillin-susceptible and oxacillin-resistant isolates. Most oxacillin-resistant *S. aureus* isolates were also resistant to gentamicin and clindamycin.

* Corresponding author.
† Present address: McMaster University, Hamilton, Ontario, Canada L8V 1C3.

TABLE 1. Comparative activities of teicoplanin and other antimicrobial agents against gram-positive blood culture isolates

Microorganism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]			% Resistant
		Range	50%	90%	
Staphylococcus aureus					
Oxacillin susceptible (131)	Teicoplanin	0.06–1.0	0.20	0.42	0
	Vancomycin	0.06–2.0	0.45	0.87	0
	Penicillin	<0.03–64	1.59	17.3	89
	Gentamicin	0.06–64	0.16	0.87	7
	Clindamycin	<0.03–>64	0.07	0.12	5
	Trimethoprim-sulfamethoxazole	<0.25/4.75–8/152	<0.25/<4.75	<0.25/<4.75	1
	Ciprofloxacin	<0.03–2.0	0.31	0.49	0
Oxacillin resistant (38)	Teicoplanin	0.12–16	0.29	0.80	0
	Vancomycin	0.5–2.0	0.74	1.0	0
	Penicillin	2.0–64	13.5	51.8	100
	Gentamicin	0.06–>64	>64	>64	87
	Clindamycin	0.06–>64	>64	>64	79
	Trimethoprim-sulfamethoxazole	<0.25/4.75–>32/608	<0.25/4.75	3/77	5
	Ciprofloxacin	0.25–64	0.29	0.48	5
Staphylococcus epidermidis					
Oxacillin susceptible (58)	Teicoplanin	0.06–4.0	0.43	0.98	0
	Vancomycin	0.06–2.0	0.76	1.0	0
	Penicillin	<0.03–8.0	0.89	3.6	80
	Gentamicin	<0.03–64	0.90	14.9	19
	Clindamycin	0.06–>64	0.11	>64	41
	Trimethoprim-sulfamethoxazole	<0.25/4.75–32/608	<0.25/4.75	5.9/111.2	33
	Ciprofloxacin	<0.03–1.0	0.14	0.24	0
Oxacillin resistant (27)	Teicoplanin	0.12–4.0	0.75	1.8	0
	Vancomycin	1.0–2.0	0.82	1.4	0
	Penicillin	2.0–64	5.5	64	100
	Gentamicin	0.06–64	10.8	25.2	67
	Clindamycin	0.06–>64	>64	>64	82
	Trimethoprim-sulfamethoxazole	<0.25/4.75–>32/608	2/38	15/285	21
	Ciprofloxacin	0.12–16	0.19	0.47	4
Staphylococcus saprophyticus					
Oxacillin susceptible (24)	Teicoplanin	<0.03–4.0	0.23	0.99	0
	Vancomycin	0.25–2.0	0.68	1.52	0
	Penicillin	<0.03–16	0.25	2.6	50
	Gentamicin	<0.03–32	0.12	7.46	1
	Clindamycin	<0.03–>64	0.05	>64	17
	Trimethoprim-sulfamethoxazole	<0.25/4.75–16/304	<0.25/<4.75	6.6/125.4	29
	Ciprofloxacin	<0.03–1.0	0.12	0.41	0
Oxacillin resistant (23)	Teicoplanin	0.12–4.0	0.47	1.3	0
	Vancomycin	1.0–2.0	0.84	1.6	0
	Penicillin	1.0–>64	8.7	27.8	100
	Gentamicin	0.06–>64	10.4	59.2	57
	Clindamycin	0.06–>64	>64	>64	83
	Trimethoprim-sulfamethoxazole	<0.25/4.75–32/608	0.38/7.12	7.4/140.6	26
	Ciprofloxacin	0.12–1.0	0.15	0.34	0
Staphylococcus hominis					
Oxacillin susceptible (12)	Teicoplanin	0.06–16	0.18	1.8	0
	Vancomycin	0.12–2.0	0.75	1.4	0
	Penicillin	<0.03–2.0	<0.03	0.9	42
	Gentamicin	<0.03–16	<0.03	7.19	8
	Clindamycin	0.03–>64	0.05	>64	17
	Trimethoprim-sulfamethoxazole	<0.25/4.75–4.0/76	<0.25/<4.75	2.8/53.2	17
	Ciprofloxacin	0.12–1.0	<0.12	0.24	0
Oxacillin resistant (11)	Teicoplanin	0.12–1.0	0.20	0.82	0
	Vancomycin	0.5–1.0	0.61	0.92	0
	Penicillin	2.0–32	8.8	15.8	100
	Gentamicin	1.0–32	4.5	15.2	18
	Clindamycin	>64	>64	>64	100
	Trimethoprim-sulfamethoxazole	<0.25/4.75–8/152	<0.25/4.75	5.8/110.2	14
	Ciprofloxacin	0.12–0.50	0.09	0.23	0

Continued on following page

TABLE 1—*Continued*

Microorganism (no. tested)	Antimicrobial agent	MIC (μg/ml)[a]			% Resistant
		Range	50%	90%	
Staphylococcus haemolyticus					
Oxacillin susceptible (9)	Teicoplanin	0.25–2.0	0.90	1.8	0
	Vancomycin	1.0–2.0	<1.0	1.7	0
	Penicillin	0.25–16	2.5	8.8	100
	Gentamicin	<0.3–0.12	<0.3	0.07	0
	Clindamycin	0.03–0.25	0.08	0.13	0
	Trimethoprim-sulfamethoxazole	<0.25/4.75–4/76	<0.25/4.75	2.2/41.8	11
	Ciprofloxacin	0.12–0.25	<0.12	0.22	0
Oxacillin resistant (21)	Teicoplanin	0.5–32	3.2	14.4	5
	Vancomycin	1.0–2.0	1.23	1.9	0
	Penicillin	4–>64	>64	>64	100
	Gentamicin	0.06–64	7.5	29.8	48
	Clindamycin	0.06–>64	>64	>64	62
	Trimethoprim-sulfamethoxazole	<0.25/4.75–16/304	3.4/65.2	10.7/202.3	15
	Ciprofloxacin	0.12–0.25	0.15	0.22	0
Enterococcus spp.					
Oxacillin susceptible (13)	Teicoplanin	0.06–0.25	0.08	0.12	0
	Vancomycin	0.06–2.0	0.61	0.98	0
	Penicillin	0.5–2.0	<0.5	0.97	0
	Gentamicin	0.5–8.0	5.0	>64	23
	Clindamycin	0.12–>64	1.75	>64	46
	Trimethoprim-sulfamethoxazole	<0.25/4.75–2/38	<0.25/<4.75	<0.25/<4.75	0
	Ciprofloxacin	0.25–4.0	0.44	1.7	8
Oxacillin resistant (60)	Teicoplanin	0.03–1.0	0.05	0.16	0
	Vancomycin	0.5–4.0	0.94	1.87	0
	Penicillin	2.5–32	2.41	3.82	3
	Gentamicin	2.0–>64	13.5	>64	72
	Clindamycin	0.12–>64	58.6	>64	98
	Trimethoprim-sulfamethoxazole	<0.25/4.75–8/152	<0.25/<4.75	0.5/9.5	2
	Ciprofloxacin	<0.03–2.0	0.45	1.25	0
Streptococcus pneumoniae, oxacillin susceptible (33)	Teicoplanin	<0.03–0.25	<0.03	0.17	0
	Vancomycin	<0.03–1.0	0.07	0.23	0
	Penicillin	<0.03–0.25	<0.03	0.08	0
	Gentamicin	<0.03–0.80	1.16	6.11	0
	Clindamycin	<0.03–0.5	<0.03	0.06	0
	Trimethoprim-sulfamethoxazole	<0.25/4.75–2/38	<0.25/<4.75	<0.25/<4.75	0
	Ciprofloxacin	<0.03–2.0	0.49	1.17	0

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

All oxacillin-susceptible strains of coagulase-negative staphylococci were susceptible to teicoplanin, vancomycin, and ciprofloxacin. The MIC ranges of both teicoplanin and vancomycin were greater for oxacillin-susceptible than for oxacillin-resistant isolates. In terms of MICs for 50 and 90% of isolates tested, gentamicin, clindamycin, and trimethoprim-sulfamethoxazole were more active against oxacillin-susceptible than oxacillin-resistant coagulase-negative staphylococci.

Teicoplanin had the greatest range of activity (0.06 to 16 μg/ml) against oxacillin-susceptible *S. hominis*. However, 11 of the 12 oxacillin-susceptible strains were inhibited by ≤1.0 μg of teicoplanin per ml; the remaining strain required 16 μg/ml for inhibition.

Most strains of *S. haemolyticus* were oxacillin resistant. The MIC for 90% of isolates tested (14.4 μg of teicoplanin per ml) was attributable to one resistant isolate and five isolates that were only marginally susceptible (MIC, 16 μg/ml) (data not presented in Table 1). All oxacillin-susceptible *S. haemolyticus* isolates were susceptible to gentamicin and clindamycin.

More than 96% of the 73 isolates of enterococci were susceptible to <16 μg of penicillin per ml. In contrast, teicoplanin and vancomycin were the only antimicrobial agents active against all enterococci tested, with teicoplanin being 8 to 12 times more potent than vancomycin for 90% of the isolates. Clindamycin and gentamicin were the least active; >64 μg/ml was required to inhibit 90% of the isolates. Of 23 strains for which MICs were >64 μg/ml, 22 had high-level resistance to gentamicin. Ciprofloxacin was active against most enterococci; only 1 of the 73 strains tested was resistant (breakpoint, ≥4 μg/ml).

S. pneumoniae was susceptible to all antimicrobial agents tested. Teicoplanin, penicillin, and clindamycin had similar ranges of activity.

Our results with bacteremic strains of gram-positive cocci support and extend the concept of cross-reactivity between teicoplanin and vancomycin; all isolates were susceptible to both agents. Although the ranges of potency were similar for oxacillin-susceptible strains of *S. aureus*, the ranges for teicoplanin were greater for oxacillin-resistant strains of *S. aureus* and all coagulase-negative staphylococci except *S. haemolyticus*. Our results concur with reports of others that certain strains of *S. haemolyticus* are less susceptible to teicoplanin than to vancomycin (1, 5, 8). Although Froggatt et al. (7) reported that isolates of *S. haemolyticus* were

resistant to multiple antimicrobial agents more frequently than other coagulase-negative staphylococci were, we found only one of nine oxacillin-susceptible strains resistant to trimethoprim-sulfamethoxazole and no other agent except penicillin. With oxacillin-resistant *S. haemolyticus* we did observe greater percentages of resistant isolates, especially for gentamicin and clindamycin. However, the percentages were no greater than for other species of coagulase-negative staphylococci. The prevalence of *S. haemolyticus* marginally susceptible to teicoplanin supports the need to identify coagulase-negative staphylococci and, in particular, strains resistant to oxacillin to the species level.

Teicoplanin was more active than vancomycin against enterococci, especially oxacillin-resistant strains. Most enterococci were resistant to gentamicin; moreover, 96% demonstrated high-level resistance. In view of the report of Moellering et al. (9) regarding species-specific resistance to combinations of aminoglycosides and cell wall-active agents, it seems unlikely that synergism between teicoplanin and gentamicin will occur with enterococcal strains that have high-level resistance to gentamicin.

Previous studies have established the in vitro potency of low concentrations of teicoplanin against *S. pneumoniae* (1, 3, 11). Teicoplanin has been reported to be eight times more active than vancomycin (11). Our data support this superior activity; moreover, teicoplanin and penicillin had identical ranges of activity, significantly lower than the interpretive standards for resistance.

Ciprofloxacin is very active against staphylococci and streptococci (2, 4, 6, 14, 15). Our data agree with these earlier reports; 0.2 to 0.5 μg of ciprofloxacin per ml inhibited 90% of the 354 bacteremic strains tested. Recent reports have provided divergent results about the activity of ciprofloxacin against enterococci. We observed that ≤1.7 μg/ml inhibited 90% of the strains tested (range, <0.03 to 4.0 μg/ml), and Fass (6) and Barry et al. (2) recorded that 2.0 μg/ml was active against 90% of their strains (range, 0.5 to 2.0 μg/ml). However, Chin and Neu (4) found the MIC for 90% of isolates tested to be 6.3 μg of ciprofloxacin per ml (range, 0.8 to 25 μg/ml). Because Chin and Neu included isolates with resistance to multiple antimicrobial agents, the presence of cross-resistance may have influenced susceptibility to ciprofloxacin.

We concluded that teicoplanin was as active as vancomycin against both oxacillin-resistant and oxacillin-susceptible strains of staphylococci, except for *S. haemolyticus*, and less active than ciprofloxacin against coagulase-negative staphylococci. Teicoplanin was the most potent of all agents tested against enterococci and demonstrated excellent activity against pneumococci.

We thank S. Grendisa and J. Wolf for skillful technical assistance and P. Radzawich for expert typing of the manuscript.

This study was supported in part by the Veterans Administration and in part by a grant from Merrell Dow Research Institute.

LITERATURE CITED

1. **Barry, A. L., R. N. Jones, T. L. Gavin, C. Thornsberry, and the Collaborative Antimicrobial Susceptibility Testing Group.** 1987. Quality control limits for teicoplanin susceptibility tests and confirmation of disk diffusion interpretive criteria. J. Clin. Microbiol. **25**:1812–1814.
2. **Barry, A. L., R. N. Jones, C. Thornsberry, L. W. Ayers, E. H. Gerlach, and H. M. Sommers.** 1984. Antibacterial activities of ciprofloxacin, norfloxacin, oxolinic acid, cinoxacin, and nalidixic acid. Antimicrob. Agents Chemother. **25**:633–637.
3. **Calain, P., K.-H. Krause, P. Vandaux, R. Auckenthaler, D. Lew, F. Waldvogel, and B. Hirschel.** 1987. Early termination of a prospective, randomized trial comparing teicoplanin and flucloxacillin for treating severe staphylococcal infections. J. Infect. Dis. **155**:187–191.
4. **Chin, N., and H. C. Neu.** 1984. Ciprofloxacin, a quinolone carboxylic acid compound active against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **25**:319–326.
5. **DelBene, V. E., J. H. John, Jr., D. A. Twitty, and J. W. Lewis.** 1986. Antistaphylococcal activity of teicoplanin, vancomycin and other antimicrobial agents: the significance of methicillin resistance. J. Infect. Dis. **154**:349–352.
6. **Fass, R. J.** 1983. In vitro activity of ciprofloxacin (Bay 09867). Antimicrob. Agents Chemother. **24**:568–574.
7. **Froggatt, J. W., J. L. Johnston, D. W. Galetto, and G. L. Archer.** 1989. Antimicrobial resistance in nosocomial isolates of *Staphylococcus haemolyticus*. Antimicrob. Agents Chemother. **33**:460–466.
8. **Low, D. E., A. McGeer, and R. Poon.** 1989. Activities of daptomycin and teicoplanin against *Staphylococcus haemolyticus* and *Staphylococcus epidermidis*, including evaluation of susceptibility testing recommendations. Antimicrob. Agents Chemother. **33**:585–588.
9. **Moellering, R. C., O. M. Korzeniowski, M. A. Sande, and C. B. Wennersten.** 1979. Species-specific resistance to antimicrobial synergism in *Streptococcus faecium* and *Streptococcus faecalis*. J. Infect. Dis. **140**:203–208.
10. **National Committee for Clinical Laboratory Standards.** 1988. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically (tentative standard), 2nd ed. Publication M7-T2. National Committee for Clinical Laboratory Standards, Villanova, Pa.
11. **Pallanza, R., M. Berti, B. P. Goldstein, E. Mapelli, E. Randisi, R. Scotti, and V. Ariole.** 1983. Teichomycin: *in vitro* and *in vivo* evaluation in comparison with other antibiotics. J. Antimicrob. Chemother. **11**:419–425.
12. **Rosenthal, S. L., and L. F. Freundlich.** 1982. An aminoglycoside disk sensitivity test for use with enterococci. J. Antimicrob. Chemother. **10**:459–462.
13. **Sahm, D. F., and C. Torres.** 1988. High-content aminoglycoside disks for determining aminoglycoside-penicillin synergy against *Enterococcus faecalis*. J. Clin. Microbiol. **26**:257–260.
14. **Sanders, C. C.** 1988. Ciprofloxacin: *in vitro* activity, mechanism of action, and resistance. Rev. Infect. Dis. **10**:516–527.
15. **Wise, R., J. M. Andrews, and L. J. Edwards.** 1983. In vitro activity of Bay 09867, a new quinolone derivative, compared with those of other antimicrobial agents. Antimicrob. Agents Chemother. **23**:559–564.