ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1990, p. 2081–2085
0066-4804/90/112081-05$02.00/0

Vol. 34, No. 11

Daptomycin Compared with Teicoplanin and Vancomycin for Therapy of Experimental *Staphylococcus aureus* Endocarditis

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Received 19 June 1990/Accepted 15 August 1990

The efficacies of daptomycin, teicoplanin, and vancomycin were compared in the therapy of experimental *Staphylococcus aureus* endocarditis. Rabbits infected with either of two methicillin-susceptible strains (SA-12871 or its moderately teicoplanin-resistant derivative SA-12873) or a methicillin-resistant *S. aureus* strain (MRSA-494) were treated with daptomycin, 8 mg/kg of body weight, every 8 h; teicoplanin, 12.5 mg/kg (low-dose teicoplanin [teicoplanin-LD], excluding MRSA-494) or 40 mg/kg (high-dose teicoplanin [teicoplanin-HD]) every 12 h; or vancomycin, 17.5 mg/kg every 6 h, for 4 days. Compared with no treatment daptomycin, teicoplamin-HD, and vancomycin significantly reduced bacterial counts of all test strains in vegetations and renal and splenic tissues ($P < 0.001$). Teicoplanin-LD was equally effective against SA-12871 but failed against SA-12873, with three of six animals still being bacteremic at the end of therapy. For SA-12871, daptomycin was as effective as teicoplanin-HD and was superior to teicoplanin-LD and vancomycin ($P = 0.02$) in lowering vegetation bacterial counts. There were no differences between daptomycin, teicoplanin-HD, or vancomycin in the reduction of bacterial counts in tissues for any of the test strains. In rabbits infected with SA-12871, vegetations from 33% of teicoplanin-LD-treated, 6% of teicoplanin-HD-treated, and 13% of daptomycin-treated animals yielded organisms for which there were up to eightfold increases in the MICs. Resistance may have contributed to early death in one daptomycin-treated animal. No increases in the MICs for the test strain were detected in animals infected with SA-12873 or MRSA-494. We conclude that in this model and against these strains of *S. aureus*, daptomycin and teicoplanin-HD are as efficacious as vancomycin, but diminished susceptibility to both can develop during therapy.

Daptomycin (LY146032) is the first of a new class of antimicrobial agents, the lipopeptides. This drug possesses excellent in vitro activity against a broad range of gram-positive bacteria and has a spectrum of activity similar to those of the glycopeptide antimicrobial agents vancomycin and teicoplanin (5, 7). However, the mechanism by which daptomycin inhibits and kills susceptible bacteria differs from those of the glycopeptides, and the drug maintains good activity against strains that are resistant to these agents (9, 11, 12, 15, 18).

The in vivo activity of daptomycin against selected gram-positive pathogens has been evaluated by using a variety of animal models and has been found to be generally good, but at times somewhat variable compared with conventional therapeutic regimens (2, 3, 10, 13, 17). The efficacy of daptomycin in the treatment of serious gram-positive infections in humans has been shown to be less than satisfactory at a dosage level of 2 mg/kg of body weight per day (6; personal communication, Eli Lilly and Co., Indianapolis, Ind.). These unsatisfactory clinical results may have been secondary to the low dosage that was used; when combined with the extensive protein binding of daptomycin (>90%; see below), this low dosage would have resulted in low concentrations of free and biologically active drug. The use of higher doses may be adequate to overcome this problem. We investigated this possibility by comparing the therapeutic activities of higher-dose daptomycin with those of vancomycin and two dosage levels of teicoplanin (another highly protein-bound drug [1]) by using the rabbit model of *Staphylococcus aureus* endocarditis. We also determined the frequencies at which test strains developed diminished susceptibility to daptomycin and teicoplanin during therapy.

MATERIALS AND METHODS

Organisms. The strains of *S. aureus* used in this study were isolates from the bloodstreams of patients with endocarditis. MRSA-494 was a methicillin-resistant *S. aureus* strain, and SA-12871 was a methicillin-susceptible strain. Strain SA-12873 was a derivative of SA-12871 that was isolated from a patient who received teicoplanin for treatment of endocarditis. The organism was significantly less susceptible to teicoplanin than the parent strain was. Additional characteristics of this organism have been described elsewhere (9).

In vitro studies. The MICs and MBCs of nafcillin, daptomycin, vancomycin, and teicoplanin for SA-12871, SA-12873, and MRSA-494 were determined by a microdilution method by using cation-adjusted Mueller-Hinton broth (CAMHB; Difco Laboratories, Detroit, Mich.) and a 1:1 combination of CAMHB and pooled normal rabbit serum (GIBCO BRL, Grand Island, N.Y.) (14). The agar dilution technique also was used to determine the MICs of daptomycin, vancomycin, and teicoplanin for each test strain (14). These data were used in the determination of spontaneous mutation frequencies (see below).

The frequencies at which test strains developed spontaneous mutational resistance to 2-, 5-, and 10-fold the daptomy-

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cin, vancomycin, or teicoplanin agar dilution MICs for the organisms were determined by exposing exponential-growth-phase organisms (~10^{10} CFU) to appropriate concentrations of each drug incorporated into Mueller-Hinton agar (Difco). Colonies were counted after 48 h of incubation at 35°C.

All isolates recovered from blood, vegetations, or tissues of animals that received daptomycin or teicoplanin were screened for the emergence of resistance to these drugs during therapy. This was done by plating undiluted blood and homogenized vegetation and tissue specimens onto Mueller-Hinton agar (Difco) containing 5- and 10-fold the appropriate agar dilution MIC. Plates were examined for growth 48 h later.

Serum protein binding. The extent of binding to human and rabbit serum proteins was determined for daptomycin, teicoplanin, and vancomycin by using a micropartition system (MPS-1; Amicon Corp., Danvers, Mass.). The micropartition device was centrifuged at 2,000 × *g* for 15 min, and the free fraction of each antimicrobial agent was expressed as the ratio of its concentration in the serum ultrafiltrate to that in whole serum multiplied by a factor of 100 (antimicrobial agent concentrations were determined as described below). Minimal adsorption of antimicrobial agents to the micropartition device was observed by using 0.85% NaCl spiked with 20 to 75 μg of vancomycin or teicoplanin per ml and 25 to 100 μg of daptomycin per ml (mean ± standard deviation recovery, 97.2 ± 0.9, 94.6 ± 1.1, and 98.0 ± 1.2%, respectively).

Animal studies. Left-sided endocarditis was established in male New Zealand White rabbits (weight, 2 to 3 kg) as described previously by using an intravenous bacterial inoculum of 10^6 (SA-12871 and MRSA-494) or 10^8 (SA-12873) CFU of the test strain (8). Eighteen hours later 1 ml of blood was withdrawn from all animals for culture. Serial dilution and plating techniques were used to determine CFU per milliliter of blood. Inclusion in the study required that this blood culture be positive and that the catheter be positioned properly across the aortic valve at the time of autopsy. Rabbits then were randomized (two to four animals per treatment group per day) to receive, for 4 days, daptomycin (8 mg/kg of body weight intravenously every 8 h), vancomycin (17.5 mg/kg intravenously every 6 h), high- or low-dose teicoplanin (teicoplanin-HD or teicoplanin-LD, respectively; 40 or 12.5 mg/kg intravenously, respectively, every 12 h; the teicoplanin-LD regimen was chosen to simulate levels found in the serum of the patient from whom SA-12873 was recovered and was not administered to rabbits infected with MRSA-494), or no treatment (controls). The dose that was administered was adjusted for weight on a daily basis. Controls were sacrificed at the time that therapy was begun in animals that received antimicrobial agents, and bacterial counts in vegetations and tissues were determined (see below).

Repeat blood samples for culture were obtained prior to the first dose on day 3. Serum samples for the measurement of peak (obtained 1 h postdose) and trough (just before a scheduled dose) antibiotic content also were obtained from all animals at this time.

After 4 days of therapy, all animals were sacrificed 10 to 12 h (for daptomycin and vancomycin) or 12 to 14 h (for teicoplanin) following the final dose and were autopsied in an aseptic manner. A terminal blood sample for culture was obtained, and vegetations and 500-mg (mean weight, representing approximately 20% of the organ) sections of the left kidney and spleen were removed for culture. These specimens were weighed, suspended in 0.85% NaCl (final volume, 1 ml), and homogenized. Quantitative bacterial counts, which were determined by serial dilution and plating techniques, were expressed as the $\log_{10}$ CFU per gram (sensitivity limit, 10 CFU per vegetation or tissue section). The effect of antibiotic carry-over on cultured material was minimized by the volume of agar used in culture plates. This dilution effect was at least 150-fold. Culture-negative specimens were considered to contain 10 CFU for numerical purposes and for comparison with other treatment regimens by one-way analysis of variance. Such specimens were considered "sterile" for comparison with other treatment regimens by use of the Fisher exact test (see below).

Antibiotic content in serum. Daptomycin concentrations in serum were determined by bioassay by using an agar well diffusion method (16); *Micrococcus luteus* ATCC 9341 was used as the indicator organism. Vancomycin and teicoplanin concentrations were determined by fluorescence polarization immunoassay (for vancomycin, TDx; Abbott Diagnostics, Irving, Tex. [19]; for teicoplanin, Innotron/American Bioclinical, Portland, Oreg. [M. J. Rybak, V. N. Reddy, G. R. Matzke, W. M. Awni, W. St. Peter, S. H. Mastin, G. D. Mayer, and M. T. Kenny, Program Abstr. 10th Annu. Meet. Am. Coll. Clin. Pharm., abstr. no. 102, 1989]). Pooled normal rabbit serum was used to prepare standards and dilute unknowns as needed.

Statistical analysis. Comparisons of bacterial counts in blood, vegetations, and tissues were made by one-way analysis of variance. Comparisons of frequencies of sterilization of these sites were made by use of the Fisher exact test. A P value of <0.05 was considered significant.

RESULTS

In vitro studies. The MICs and MBCs of nafcillin, daptomycin, teicoplanin, and vancomycin for each test strain in CAMHB and a 1:1 combination of CAMHB-pooled normal rabbit serum are given in Table 1. For each organism, agar dilution MICs were similar to the microdilution results found in CAMHB. The presence of serum in the test medium affected the activities of daptomycin and teicoplanin to a greater degree than it did those of vancomycin or nafcillin, with the single exception of vancomycin versus MRSA-494. Table 1 also shows the frequencies of spontaneous mutational resistance to various multiples of the daptomycin, teicoplanin, and vancomycin MICs for each of the test strains.

Protein binding studies. Daptomycin was found to be 97 and 96% bound to rabbit and human serum proteins, respectively. The corresponding results for teicoplanin were 91 and 90%, and for vancomycin they were 43 and 47%.

Animal studies. No differences were found in the intensity of pretreatment bacteremia (mean ± standard deviation $\log_{10}$ CFU per milliliter) for animals infected with SA-12871 and receiving daptomycin (3.25 ± 0.76), teicoplanin-HD (2.85 ± 1.04), teicoplanin-LD (2.61 ± 1.01), or vancomycin (3.18 ± 0.84) sacrificed after 4 days of therapy or controls sacrificed 18 h after bacterial challenge (3.08 ± 1.01). The same was true for those infected with MRSA-494 and treated with daptomycin (2.79 ± 0.72), teicoplanin-HD (2.67 ± 0.60), vancomycin (3.06 ± 0.58), or controls (3.08 ± 0.80). For SA-12873, the degree of pretreatment bacteremia of animals treated with teicoplanin-LD (1.51 ± 0.55) was significantly lower than that found in animals that received the other treatment regimens (daptomycin, 2.73 ± 0.66, $P < 0.002$; teicoplanin-HD, 2.60 ± 0.75, $P < 0.005$; vancomycin, 2.55 ±

TABLE 1. In vitro study results

Test strain and antimicrobial agent	CAMHB		CAMHB-PNRS[a]		Mutation frequency at the following selecting concn[b]:		
	MIC (μg/ml)	MBC (μg/ml)	MIC (μg/ml)	MBC (μg/ml)	2	5	10
SA-12871							
Nafcillin	1.2	1.6	1.1	1.1	ND[c]	ND	ND
Daptomycin	0.4	0.5	3.1	5.3	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
Teicoplanin	0.8	1.7	3.1	6.3	9.3×10^{-7}	1.9×10^{-8}	1.6×10^{-9}
Vancomycin	0.7	1.0	1.1	1.6	3.1×10^{-7}	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
SA-12873							
Nafcillin	1.6	1.6	1.9	1.9	ND	ND	ND
Daptomycin	0.4	0.4	3.7	6.3	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
Teicoplanin	13.4	19.8	35.4	50.0	3.2×10^{-8}	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
Vancomycin	1.5	2.2	2.6	3.1	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
SA-494							
Nafcillin	21.0	45.9	25.0	42.0	ND	ND	ND
Daptomycin	0.2	0.2	3.1	3.1	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$
Teicoplanin	0.5	1.4	2.6	3.7	2.5×10^{-6}	1.1×10^{-7}	1.0×10^{-9}
Vancomycin	0.4	0.4	1.1	1.1	2.0×10^{-9}	$<1 \times 10^{-10}$	$<1 \times 10^{-10}$

[a] CAMHB-PNRS, 1:1 combination of CAMHB and pooled normal rabbit serum.
[b] The selecting concentration was the indicated multiple of the appropriate agar dilution MIC.
[c] ND, Not determined.

0.49, $P < 0.001$; control, 2.92 ± 0.52, $P < 0.001$), possibly due, in part, to the small number of animals in this group. There were no differences between rabbits that received daptomycin, teicoplanin-HD, vancomycin, or no treatment (controls).

The concentrations achieved in serum with each of the treatment regimens are given in Table 2. There were no differences in the frequencies of blood culture sterilization after 2 or 4 days of therapy with daptomycin, teicoplanin-HD, teicoplanin-LD (excluding MRSA-494), or vancomycin in animals infected with SA-12871 or MRSA-494. Regardless of the treatment regimen used, 93 to 100% of rabbits had sterile cultures at both of these times. For rabbits infected with SA-12873, 88 to 94% had sterile blood cultures after 2 and 4 days of therapy with daptomycin, teicoplanin-HD, or vancomycin. The teicoplanin-LD regimen was as effective as the other regimens after 2 days of therapy (67% of blood cultures were sterilized), but after 4 days it was inferior to teicoplanin-HD (50 versus 94%, respectively; $P < 0.05$).

TABLE 2. Antimicrobial agent concentrations in serum

Infecting strain and treatment	Mean ± SD concn in serum (μg/ml)	
	Peak	Trough
SA-12871		
Daptomycin	82.9 ± 6.9	21.8 ± 4.3
Teicoplanin-HD	187.6 ± 30.2	31.8 ± 11.6
Teicoplanin-LD	42.5 ± 8.8	6.2 ± 3.2
Vancomycin	29.0 ± 5.2	4.6 ± 6.7
SA-12873		
Daptomycin	70.6 ± 16.6	18.9 ± 7.4
Teicoplanin-HD	163.9 ± 25.6	30.8 ± 10.4
Teicoplanin-LD	42.4 ± 6.3	5.7 ± 1.9
Vancomycin	24.0 ± 4.9	2.9 ± 2.0
SA-494		
Daptomycin	77.2 ± 10.2	20.5 ± 5.6
Teicoplanin-HD	196.8 ± 22.5	37.2 ± 9.8
Vancomycin	26.0 ± 5.6	3.2 ± 2.0

Quantitative bacterial counts found in vegetations and tissues are given in Table 3. Only a single animal (infected with SA-12871 and treated with daptomycin) died before completion of the 4-day treatment course (see below). For rabbits infected with SA-12871 or MRSA-494, there were highly significant reductions in bacterial counts compared with those for untreated controls at each site from which samples were taken for culture for all treatment regimens ($P < 0.001$). For animals infected with SA-12873, treatment with daptomycin, teicoplanin-HD, or vancomycin significantly reduced bacterial counts at all sites ($P < 0.001$). Treatment with teicoplanin-LD reduced bacterial counts in kidneys ($P < 0.002$) and spleens ($P < 0.02$), but not in vegetations ($P > 0.05$).

For animals infected with SA-12871, daptomycin was as effective as teicoplanin-HD and was more effective than teicoplanin-LD or vancomycin ($P < 0.02$) in reducing vegetation bacterial counts. There were no differences between daptomycin, teicoplanin-HD, or vancomycin for other sites from which samples were taken for culture or for animals infected with SA-12873 or MRSA-494. The teicoplanin-LD regimen was inferior to the daptomycin regimen in lowering vegetation bacterial counts in animals infected with SA-12873 ($P < 0.005$); compared with teicoplanin-HD and vancomycin, statistical significance was not achieved ($P = 0.06$ for both). With respect to renal tissue, the teicoplanin-LD regimen was inferior to the daptomycin ($P < 0.05$) and vancomycin ($P < 0.01$) regimens. This regimen was inferior to all other treatment regimens in reducing splenic bacterial counts ($P < 0.005$ versus daptomycin and teicoplanin-HD and $P < 0.02$ versus vancomycin).

Daptomycin was superior to teicoplanin-HD ($P = 0.04$), teicoplanin-LD ($P = 0.008$), and vancomycin ($P = 0.004$) in sterilizing vegetations of rabbits with SA-12871 endocarditis. There were no differences between treatment regimens with respect to sterilization of renal or splenic tissue in animals infected with this strain. For animals infected with SA-12873, no regimen was clearly superior in its ability to sterilize vegetations or kidneys; however, daptomycin was superior to teicoplanin-LD in the sterilization of splenic

TABLE 3. Bacterial counts in vegetation and tissue

Infecting strain and treatment	No. of rabbits	Bacterial counts (mean ± SD $\log_{10}$ CFU/g) in [a]:		
		Vegetation	Kidney	Spleen
SA-12871				
Daptomycin	16	3.32 ± 1.91 (11)	1.12 ± 0.09 (14)	1.22 ± 0.12 (14)
Teicoplanin-HD	16	4.30 ± 1.52 (5)	1.12 ± 0.09 (16)	1.22 ± 0.12 (16)
Teicoplanin-LD	9	5.82 ± 2.65 (1)	1.05 ± 0.07 (9)	1.30 ± 0.28 (7)
Vancomycin	14	5.24 ± 2.20 (2)	1.30 ± 0.62 (11)	1.29 ± 0.38 (12)
None (control)	10	9.74 ± 0.49 (0)	6.02 ± 1.50 (0)	5.87 ± 0.67 (0)
SA-12873				
Daptomycin	16	4.14 ± 1.09 (3)	1.30 ± 0.73 (14)	1.16 ± 0.09 (16)
Teicoplanin-HD	16	4.59 ± 2.37 (6)	1.41 ± 1.23 (15)	1.18 ± 0.28 (15)
Teicoplanin-LD	6	7.07 ± 3.28 (1)	2.35 ± 1.63 (3)	3.01 ± 2.16 (3)
Vancomycin	16	4.56 ± 2.35 (5)	1.17 ± 0.27 (15)	1.38 ± 0.73 (14)
None (control)	10	9.02 ± 0.70 (0)	5.24 ± 1.09 (0)	4.98 ± 0.47 (0)
SA-494				
Daptomycin	17	2.43 ± 0.30 (17)	1.08 ± 0.10 (17)	1.25 ± 0.09 (17)
Teicoplanin-HD	15	2.87 ± 0.85 (12)	1.15 ± 0.05 (15)	1.18 ± 0.08 (15)
Vancomycin	18	3.01 ± 1.56 (14)	1.27 ± 0.52 (17)	1.44 ± 0.61 (17)
None (control)	10	8.79 ± 0.89 (0)	5.65 ± 1.86 (0)	5.37 ± 0.80 (0)

[a] Values in parentheses are the number of culture-negative (sterile) specimens.

tissue ($P = 0.01$). All regimens were equivalent with respect to sterilization of each of the sites from which samples were taken for culture in animals infected with MRSA-494.

In vivo development of resistance. Isolates of SA-12871 for which there were two- to fourfold rises in the teicoplanin MICs were recovered from the vegetations of 3 of 9 rabbits treated with teicoplanin-LD and 1 of 16 rabbits treated with teicoplanin-HD. These organisms made up 0.0006 to 0.003 and 81% of organisms recovered from the vegetations of animals treated with teicoplanin-LD and teicoplanin-HD, respectively. Isolates for which there were four- to eightfold rises in the daptomycin MICs were recovered from 2 of 16 rabbits treated with that drug. One of these animals died after receiving 10 of a planned 12 doses; postmortem examination demonstrated a persistence of organisms in blood, vegetations, and tissues. Blood and vegetation material yielded the resistant organisms, and resistant isolates made up the majority of the bacteria recovered from these sites. For the second animal, a single isolate for which there was a fourfold rise in the daptomycin MIC was recovered from vegetation material (0.008% of the total number of CFU recovered from that site). All isolates of SA-12871 for which there were rises in the daptomycin or teicoplanin MICs were recovered from plates containing 5- to 10-fold the MIC for the organism, but few maintained the expected degree of resistance after a single passage in antibiotic-free medium. The increments in MICs reported above were stable following several such passages.

No increases in daptomycin or teicoplanin MICs were found for posttherapy isolates of SA-12873 or MRSA-494.

DISCUSSION

Glycopeptide antimicrobial agents are useful alternatives to β-lactams in patients with infections caused by such organisms as methicillin-resistant staphylococci or β-lactamase-producing enterococci or in those patients who have significant β-lactam allergies. Based on its spectrum of activity and results of animal studies, it appeared to be likely that the lipopeptide daptomycin would perform in a similar fashion. Daptomycin possesses an advantage over the glycopeptides in that it maintains good activity against strains resistant to vancomycin and teicoplanin (9, 11, 12, 15, 18). However, as with teicoplanin, early data from human trials have been disappointing (4, 6). Because of the highly protein-bound nature of both drugs, inadequate dosing in these trials may have been the main reason for the unsatisfactory results that were observed. In the current study we used doses of teicoplanin that produced levels in serum similar to those being achieved during therapy of serious systemic human staphylococcal infections (personal communication, Merrell-Dow Research Institute, Cincinnati, Ohio) and a dose of daptomycin that produced peak levels in serum moderately above those targeted for humans (40 to 60 μg/ml at the end of infusion; personal communication, Eli Lilly and Co.). We found that compared with untreated control animals, all treatment regimens that we used (including teicoplanin-LD) significantly reduced bacterial counts in vegetations and tissues of rabbits infected with SA-12871 or MRSA-494. With the exception of the teicoplanin-LD regimen, the same was true for animals infected with SA-12873, the moderately teicoplanin-resistant strain. In this case the teicoplanin-LD regimen likely failed because of the low concentration achieved in serum, which, when combined with the extensive protein binding of teicoplanin, resulted in free drug levels below the MIC for the organism throughout the dosing interval. Indeed, even in the presence of only 50% serum, we found that the teicoplanin MIC and MBC for SA-12873 rose to concentrations approximately 17% below and above, respectively, the peak concentration of the drug achieved in animals infected with this test strain. Based on MIC and MBC determinations in the presence of 50% serum and the degree of serum protein binding that we found, levels of free drug in serum likely exceeded the MIC (and in most cases the MBC) over the entire dosing interval with each of the other treatment regimens for this and the other two test strains.

For each of the test strains of *S. aureus* we used, daptomycin and teicoplanin-HD were equivalent, and in some cases daptomycin was superior, to the other regimens that we tested in reducing (or sterilizing) vegetation bacterial

counts. However, diminished susceptibility to both daptomycin and teicoplanin was found in isolates of SA-12871 from rabbits treated with either drug. The occurrence of reduced susceptibility to teicoplanin was more frequent in teicoplanin-LD-treated rabbits than it was in those treated with teicoplanin-HD. Resistant organisms probably were selected for by the presence of low concentrations of drug deep within vegetations. It is likely that a similar phenomenon occurred in the patient from whom SA-12873 was recovered. Teicoplanin dosing regimens currently in use in human clinical trials result in concentrations in serum comparable to those we observed in this study and, similar to our findings with the teicoplanin-HD regimen, may reduce the likelihood of resistance arising in vivo. Of great interest was the fact that spontaneous mutants of SA-12871 that expressed resistance to teicoplanin similar to that found in SA-12873 were detectable in vitro, whereas mutants resistant to even low levels of daptomycin were not. It may be that resistance to daptomycin requires multiple mutations, which could occur during prolonged exposure to intravegetation organisms to subinhibitory concentrations of the drug.

Even though MRSA-494 had spontaneous frequencies of mutation to teicoplanin resistance that were similar to those of SA-12871 in vitro, no posttherapy isolates of MRSA-494 showing diminished susceptibility to the drug were found. We observed that vegetations in animals infected with MRSA-494 were, on average, 50% smaller than those of animals infected with SA-12871. This phenomenon might explain the greater reduction in vegetation bacterial counts seen for treated rabbits with MRSA-494 endocarditis compared with those infected with SA-12871. It also may have resulted in intravegetation drug concentrations high enough to cause rapid elimination of vegetation-associated organisms and thus a reduced likelihood of the development of resistance. Indeed, 80% of rabbits infected with MRSA-494 and treated with teicoplanin-HD had culture-negative (sterile) vegetations, compared with 11 and 31% of the rabbits infected with SA-12871 and treated with teicoplanin-LD and teicoplanin-HD, respectively.

In conclusion, we have established that, in the rabbit model and against the *S. aureus* test strains we used, daptomycin and teicoplanin-HD are as efficacious as vancomycin, but for certain strains of *S. aureus*, diminished susceptibility to both can develop during therapy. The results of human clinical trials being conducted with both drugs should establish whether this effectiveness in an animal model extends to human infections with *S. aureus*. It is likely that extensive clinical use will be required to establish whether or not resistance to either drug will be a major clinical problem, but our findings in this animal model raise some concern regarding the possibility.

ACKNOWLEDGMENTS

This study was supported by a grant from Eli Lilly and Co.
We thank Frederic Smith for technical assistance.

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