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Comparative Efficacy of Daptomycin, Vancomycin, and Cloxacillin for the Treatment of *Staphylococcus aureus* Endocarditis in Rats and Role of Test Conditions in This Determination

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The in vivo efficacy of daptomycin, a new cell wall-active anti-gram-positive-bacterial agent, was compared to those of cloxacillin and vancomycin in a rat model of *Staphylococcus aureus* endocarditis. Both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) strains were used. When therapy was initiated early (8 h) after infection, at the time when valvular bacterial counts were relatively low (approximately 10^6 CFU/g of vegetation), 3 days of therapy was found to be effective against the MSSA strains whatever the antibiotic regimen. In contrast, when the onset of therapy was delayed up to 15 h after infection, so that higher bacterial counts could develop on the valves (approximately 10^9 CFU/g of vegetation), a longer period of treatment (6 days) was required to cure infection. Under these conditions after 3 days of therapy, daptomycin was more effective than cloxacillin and vancomycin against the MSSA strains. Similarly, daptomycin showed a greater activity than vancomycin against the MRSA strain after 3 days of treatment, but after 6 days both antibiotics were equally effective. Decreasing doses of daptomycin showed decreasing activity: 10 mg/kg of body weight every 12 h (q12h) was better than 5 mg/kg q12h, whereas 5 mg/kg q24h (providing drug levels in blood detectable only during the first 12 h) failed to cure infection. In vitro, daptomycin was highly bactericidal at high concentrations (25 and 60 μg/ml, corresponding to peak levels in serum after doses of 5 and 10 mg/kg, respectively) and bacteriostatic at lower concentrations (0.5 to 2.5 μg/ml, corresponding to trough levels in serum). In conclusion, against low-bacterial-count *S. aureus* endocarditis, daptomycin showed an efficacy similar to those of vancomycin and cloxacillin. Against high-bacterial-count *S. aureus* endocarditis, daptomycin showed a higher bactericidal activity than cloxacillin (against the MSSA strains) and vancomycin (against both the MSSA and MRSA strains).

Daptomycin is a recently developed antibacterial biosynthetic agent which belongs to a new class of antibiotics known as lipopeptides (M. Debono, B. J. Abbott, V. M. Krupinski, R. M. Molloy, D. R. Berry, F. T. Counter, L. C. Howard, J. L. Ott, and R. L. Hamill, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1077, 1984). In vitro susceptibility data indicate excellent bactericidal activity against gram-positive aerobic and anaerobic organisms, with the exception of *Listeria monocytogenes* (3, 12). MICs of daptomycin are similar to or lower than those of vancomycin for most of the gram-positive cocci and particularly for *Enterococcus faecalis*, *Staphylococcus epidermidis*, and methicillin-resistant *Staphylococcus aureus* (MRSA). The pharmacokinetic profile of this new compound in animals shows a prolonged half-life in serum that reaches 2.2 h in rats (H. W. Culp, W. D. Daniels, M. Debono, R. M. Gale, R. L. Hamill, L. C. Howard, R. M. Molloy, and H. R. Papiska, 26th ICAAC, abstr. no. 893, 1986). Until now daptomycin has been tested in vivo in rats in models of *E. faecalis* chronic hematogenous pyelonephritis (9), subcutaneous *S. aureus* abcesses (C. A. Wood, H. C. Finkbeiner, S. J. Kohlhepp, and D. N. Gilbert, 26th ICAAC, abstr. no. 822, 1986), and *E. faecalis* endocarditis (2). In these three animal models, daptomycin showed a good therapeutic efficacy when compared with those of classic agents such as vancomycin. In a rabbit model of aortic valve endocarditis due to group G streptococci, daptomycin was as effective as penicillin G in eradicating bacteria from vegetations (1). For treatment of rabbit endocarditis due to *S. aureus* or *S. epidermidis*, daptomycin (10 mg/kg of body weight as a single daily dose) was equally effective as or better than a standard nafcillin or vancomycin regimen (7). Considering its high in vitro bactericidal activity, particularly against *S. aureus*, and its pharmacokinetic properties, daptomycin appears to be a potential agent for the treatment of severe *S. aureus* infections such as endocarditis. The purpose of the present study was to determine the in vivo efficacy of daptomycin and to compare it with those of cloxacillin and vancomycin in a rat model of *S. aureus* endocarditis due to both methicillin-susceptible *S. aureus* (MSSA) and MRSA strains.

(This work was presented in part at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy [L. Cantoni, M. P. Glauser, and J. Bille, 27th ICAAC, abstr. no. 165, 1987].)

MATERIALS AND METHODS

Microorganisms. Three different strains of *S. aureus* isolated from three different patients with bacterial endocarditis were used: two methicillin-susceptible strains (MSSA1 and MSSA2), and one methicillin-resistant strain (MRSA3).

Susceptibility studies. For the three *S. aureus* strains, MICs and MBCs of daptomycin, vancomycin, and cloxacillin were determined by a broth macrodilution method (6) using an inoculum of 5×10^5 organisms per ml from an overnight culture in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.). For daptomycin, Mueller-Hinton broth

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supplemented with 50 mg of calcium per liter and 25 mg of magnesium per liter was used. Indeed, a calcium concentration corresponding to the physiological calcium level in serum is required to allow expression of daptomycin activity (3). MIC reading was performed after 24 h of incubation at 35°C. The MBC was defined as the lowest concentration of antibiotic which killed 99.9% of the initial inoculum after 24 h of incubation.

Experiments to determine killing curves were done in triplicate in tryptic soy broth (Difco Laboratories) with inocula of 10^5 and 10^7 CFU/ml, with cation supplementation for daptomycin, at concentrations of daptomycin and vancomycin corresponding to 2× the MIC, 10× the MIC, and the peak and trough levels of both drugs in serum measured in treated animals. A volume of 0.5 ml of each sample as well as 10- and 100-fold dilutions was plated on Columbia blood agar plates with an automatic device (Spiral System DS; Interscience, Saint-Nom, France). This subculture procedure permits reduction of carry-over of antibiotics (8). Colonies were counted after 48 h of incubation at 37°C. MIC determinations were done for the bacteria surviving daptomycin exposure for 24 and 48 h.

Production of endocarditis. Sterile vegetations were produced in female Wistar rats (180 to 200 g) by a modification of a method already described (5). Briefly, a polyethylene catheter (PP 10; Portex Ltd., Hythe, Kent, England) was inserted across the aortic valve through the right carotid artery and secured with a silk ligature. Four days after catheterization, the rats were injected in the tail vein with 0.5 ml of saline containing 10^5 CFU of *S. aureus* (MSSA1, MSSA2, and MRSA3). The catheter was left in place throughout the experiments.

Evaluation of infection. In order to determine the incidence and the magnitude of valvular infection as well as the incidence of positive blood cultures, control rats chosen at random were sacrificed 8 or 15 h after intravenous injection of *S. aureus*, i.e., at the time the treatment was started in the test rats. Treated rats were sacrificed after 3 or 6 days of treatment when no antibiotic activity was detectable in blood, i.e., at least 12 h after the last injection of vancomycin or cloxacillin or 24 h after the last injection of daptomycin. One milliliter of blood was drawn from the inferior vena cava, plated on blood agar, and incubated for colony counts. Aortic vegetations were excised, weighed, homogenized in 1 ml of saline, and serially diluted and plated. Plates were counted after 24 h of incubation at 37°C, and the results were expressed as $\log_{10}$CFU per gram of vegetation. This method permitted the detection of 10^2 CFU/g of tissue. Bacteria recovered from the vegetations of treated rats were stored at −20°C or tested immediately for subsequent MIC determinations. Rats that died during treatment were refrigerated at 4°C within 6 h of death; blood was not cultured from these animals, but vegetations were processed as described above. Rats that died before having received less than 75% of the treatment regimen were not taken into account in the final evaluation of bacterial counts on the vegetations.

Treatment of *S. aureus* endocarditis with various antibiotic regimens. Treatment with antibiotic was started 8 h after infection for the MSSA1 and MSSA2 strains (half of the experiments) and 15 h after infection for the MSSA2 (half of the experiments) and MRSA3 strains. Daptomycin (Eli Lilly Laboratories, Indianapolis, Ind.) was reconstituted in a buffer solution and injected subcutaneously at various doses (see Tables 1 to 3). Treatment was performed for 3 or 6 days. Vancomycin (injectable; 500-mg vial; Lilly) as well as cloxacillin (Orbenin; injectable; 1-g vial; Beecham Research Laboratories, Brockham Park, England) was diluted in saline and given subcutaneously at various doses (see Tables 1 to 3).

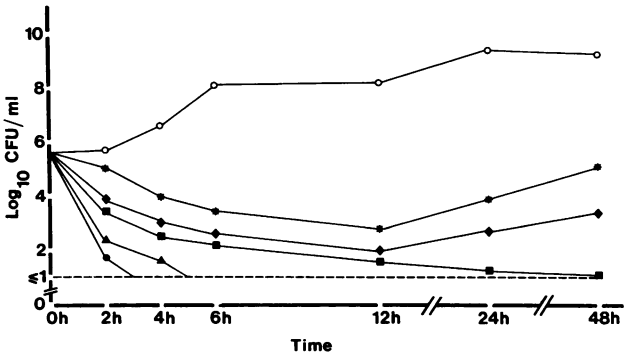

FIG. 1. Time kill studies showing the activity of daptomycin against *S. aureus* MSSA2 at 0.5 μg/ml (*; a drug concentration equal to 2× the MIC), 2.5 μg/ml (◆; a drug concentration equal to 10× the MIC and to the trough level in sera of rats receiving a 5-mg/kg dose), 5 μg/ml (■; a drug concentration equal to the trough level in sera of rats receiving a 10-mg/kg dose), 25 μg/ml (▲; a drug concentration equal to the peak level in sera of rats receiving a 5-mg/kg dose), and 60 μg/ml (●; a drug concentration equal to the peak level in sera of rats receiving a 10-mg/kg dose), and without antibiotics (○; control). Similar results were observed in time kill studies of MSSA1 and MRSA3 (see text).

Serum antibiotic levels. Levels of cloxacillin, vancomycin, and daptomycin in serum were determined in normal rats at various intervals after one subcutaneous injection and measured by microbiological assay using a test strain of *Bacillus subtilis* (Subtilis spore suspension; Difco Laboratories) for vancomycin and cloxacillin and a test strain of *Sarcina lutea* (ATCC 9341) for daptomycin. To determine whether accumulation of drug occurred during treatment, additional serum antibiotic level measurements were performed after cumulative doses of daptomycin and of vancomycin in infected animals (3 and 6 days of therapy with the various regimens).

Statistical evaluation. The chi-square test with Yates' correction was used for the comparison of the sterilization of vegetations. Nonparametric analysis with the Wilcoxon Mann-Whitney test was used for the comparison of the bacterial counts in the vegetations. The Bonferroni correction was used for multiple comparisons.

RESULTS

Susceptibility studies. The MIC and MBC (in micrograms per milliliter) of daptomycin, vancomycin, and cloxacillin for the three different strains used in vivo were as follows: for MSSA1, daptomycin—0.25 and 0.5, vancomycin—1.0 and 2.0, and cloxacillin—0.25 and 64; for MSSA2, daptomycin—0.25 and 0.5, vancomycin—1.0 and 8.0, and cloxacillin—2.0 and 64; and for MRSA3, daptomycin—0.25 and 2.0, vancomycin—1.0 and 2.0, and cloxacillin—64 and 512.

The time kill studies of strain MSSA2 done with an inoculum of 10^5 CFU/ml with daptomycin are reported in Fig. 1. As can be seen, the bactericidal activity was dose dependent upon exposure to daptomycin. With concentrations of daptomycin corresponding to peak serum daptomycin levels after the 5- and 10-mg/kg doses (25 and 60 μg/ml, respectively), the initial inoculum was killed within 6 h. This phenomenon was apparently not related to the carry-over of

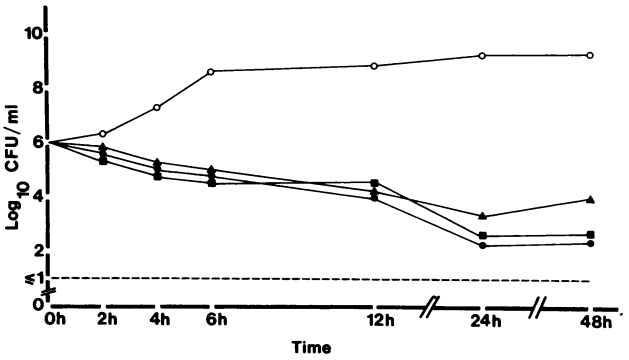

FIG. 2. Time kill studies showing the activity of vancomycin against *S. aureus* MSSA2 at 2 μg/ml (▲; a drug concentration equal to 2× the MIC and to the trough level in sera of rats receiving a 30-mg/kg dose), 10 μg/ml (■; a drug concentration equal to 10× the MIC), and 40 μg/ml (●; a drug concentration equal to the peak level in sera of rats receiving a 30-mg/kg dose), and without antibiotics (○; control). Similar results were observed in time kill studies of MSSA1 and MRSA3 (see text).

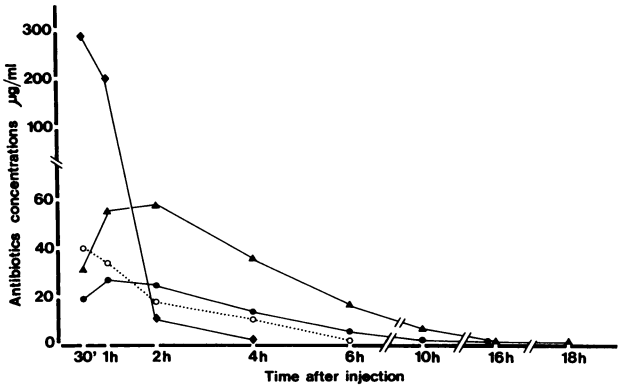

FIG. 3. Antibiotic levels in rat serum after a single subcutaneous injection of daptomycin (10 [▲] or 5 [●] mg/kg), vancomycin (30 mg/kg [○]), or cloxacillin (200 mg/kg [◆]). Each point represents the mean of values from three to six rats.

antibiotics when high concentrations of daptomycin were tested because special care was taken to avoid this phenomenon. A slower fall in viable counts was observed after exposure to low concentrations of daptomycin (equal to 2× and 10× the MIC), and regrowth occurred at 24 h. Similar results were observed with an inoculum of 10^7 CFU/ml and with strain MSSA1 (data not shown). Time kill studies of the methicillin-resistant strain MRSA3 with daptomycin (not represented in Fig. 1) showed a bactericidal activity that was also dose dependent upon exposure to daptomycin but was less pronounced than with the two methicillin-susceptible strains; with concentrations corresponding to peak levels in serum after the 5- and 10-mg/kg doses, decreases of 3 to 4 and of 4 to 5 $\log_{10}$CFU/ml, respectively, were seen within 6 and 12 h, and the whole bacterial inoculum was killed within 48 h. The MICs for the bacteria surviving daptomycin exposure for 24 and 48 h ranged from 0.5 to 2 μg/ml, i.e., they were similar to those in the original inoculum.

The bactericidal activities of vancomycin were similar for the three strains used and were less pronounced than that of daptomycin (Fig. 2 shows results for MSSA2). In particular, complete killing could not be achieved in test tubes despite concentrations of vancomycin simulating peak levels in serum.

Serum antibiotic levels. Serum antibiotic levels in noninfected animals after a single injection of 30 mg of vancomycin per kg, 10 or 5 mg of daptomycin per kg, or 200 mg of cloxacillin per kg are shown in Fig. 3. In animals with endocarditis, no detectable drug was found in the blood ≥16 h after cumulative doses of daptomycin for 3 or 6 days of therapy.

Comparative efficacy of various treatment regimens. (i) Efficacy of antibiotic treatment started early after establishment of endocarditis induced by MSSA strains. The severity of valvular infection due to strain MSSA1 in control rats sacrificed at the start of treatment (i.e., 8 h postinfection) is reported in Table 1. As can be seen, the bacterial counts on the vegetations were relatively low (median, 5.82 $\log_{10}$ CFU/g of vegetation) when treatment was started after this short period of incubation. All three therapeutic regimens were highly effective in reducing the incidence and magnitude of valvular infection due to strain MSSA1. The efficacy of the regimen consisting of daptomycin every 12 h (q12h) was comparable with that of the 30-mg/kg q12h vancomycin regimen. The 200-mg/kg q5h cloxacillin regimen was as effective as the 30-mg/kg q12h vancomycin regimen. Similar results were observed when the treatment of endocarditis due to strain MSSA2 started early (8 h) after bacterial challenge was tested, when the bacterial counts on the vegetation were low (median, 6.42 $\log_{10}$CFU/g of vegetation). Despite only 3 days of treatment, the 30-mg/kg q6h vancomycin regimen resulted in 80% of aortic valve vegetations being sterile, an efficacy significantly better than that obtained after 6 days of therapy with vancomycin started late (15 h) after bacterial challenge (see Table 2).

(ii) Efficacy of antibiotic treatment started late after establishment of endocarditis induced by strains MSSA2 and MRSA3. In order to detect possible differences in the efficacies of the various antibiotic regimens, experiments in which treatment was delayed for 15 h after infection were performed with MSSA2, so that control rats sacrificed at this

TABLE 1. Comparative efficacies of daptomycin, vancomycin, and cloxacillin for the early (8 h) treatment of MSSA1 endocarditis

Regimen	Results with short treatment (3 days)		
	No. of evaluable rats[a]/total no. of rats[b]	% Evaluable rats[a] with sterile vegetations	Median $\log_{10}$ CFU/g of vegetation (range)[c]
Control	35[d]	6	5.82 (<2–8.6)a
Vancomycin (30 mg/kg q12h)	18/18	67	<2 (<2–9.8)b
Daptomycin (10 mg/kg q12h)	11/11	91	<2 (<2–4.35)c
Cloxacillin (200 mg/kg q5h)	27/27	93	<2 (<2–3.55)d

[a] Number of rats sacrificed at completion of treatment + number of rats that died after receiving ≥75% of total treatment.

[b] Number of rats in each group at the beginning of treatment.

[c] Statistical comparisons: a and b, $P < 10^{-2}$; a and c, $P < 10^{-5}$; a and d, $P < 10^{-10}$. All other differences are not statistically significant.

[d] Number of rats sacrificed at the beginning of treatment (control rats), i.e., 8 h after induction of infection.

TABLE 2. Comparative efficacies of daptomycin, vancomycin, and cloxacillin for delayed (15 h postinfection) treatment of MSSA2 endocarditis

Regimen	No. of evaluable rats[a]/total no. of rats[b]	% Evaluable rats[a] with sterile vegetations	Median $\log_{10}$ CFU/g of vegetation (range)[c]
Short treatment (3 days)			
Control	33[d]	0	9.14 (6.43–10.3)a
Vancomycin (30 mg/kg q12h)	17/23	12	8.65 (<2–10.7)b
Daptomycin (10 mg/kg q12h)	20/21	35	3.65 (<2–7)c
Long treatment (6 days)			
Control	33[d]	0	9.14 (6.43–10.3)a
Vancomycin			
30 mg/kg q6h	15/21	33	3.37 (<2–9.6)d
30 mg/kg q12h	10/11	30	7.87 (<2–9.54)e
Daptomycin			
10 mg/kg q12h	21/22	81	<2 (<2–4.4)f
10 mg/kg q24h	10/11	60	<2 (<2–10)g
5 mg/kg q12h	18/23	50	2.6 (<2–10.04)h
5 mg/kg q24h	10/12	0	8.3 (5.24–9.8)i
Cloxacillin (200 mg/kg q5h)	7/17	43	3.51 (<2–5.11)j

[a] See Table 1, footnote *a*.
[b] See Table 1, footnote *b*.
[c] Statistical comparisons were as follows. For 3 days of therapy: a and c, $P < 10^{-3}$; b and c, $P < 10^{-3}$. For 6 days of therapy: a and d, $P < 10^{-3}$; a and f, $P < 10^{-9}$; a and g, $P < 10^{-3}$; a and h, $P < 10^{-4}$; a and j, $P < 10^{-4}$; d and f, $P < 10^{-2}$; e and f, $P < 10^{-3}$; f and i, $P < 10^{-5}$; i and j, $P < 10^{-3}$. All other differences are not statistically significant.
[d] Number of rats sacrificed at the beginning of treatment (15 h after induction of infection).

TABLE 3. Comparative efficacies of daptomycin, vancomycin, and cloxacillin for delayed (15 h postinfection) treatment of MRSA3 endocarditis

Regimen	No. of evaluable rats[a]/total no. of rats[b]	% Evaluable rats[a] with sterile vegetations	Median $\log_{10}$ CFU/g of vegetation (range)[c]
Short treatment (3 days)			
Control	20[d]	0	8.50 (6.51–9.45)a
Vancomycin (30 mg/kg q12h)	14/15	0	9.25 (4.17–10.4)b
Daptomycin (10 mg/kg q12h)	14/15	14	5.20 (<2–9.36)c
Long treatment (6 days)			
Control	20[d]	0	8.50 (6.51–9.45)a
Vancomycin (30 mg/kg q6h)	15/18	53	<2 (<2–10.12)d
Daptomycin			
10 mg/kg q12h	17/18	61	<2 (<2–9.54)e
10 mg/kg q24h	8/8	75	<2 (<2–10.34)
5 mg/kg q12h	17/22	29	7.05 (<2–10.24)

[a] See Table 1, footnote *a*.
[b] See Table 1, footnote *b*.
[c] Statistical comparisons were as follows. For 3 days of therapy: a and c, $P < 10^{-3}$; b and c, $P < 10^{-2}$. For 6 days of therapy: a and d, $P < 10^{-3}$; a and e, $P < 10^{-4}$.
[d] Number of rats sacrificed at the beginning of treatment (15 h after induction of infection).

time had 9.14 $\log_{10}$CFU/g of vegetation (Table 2). This allowed us to investigate a 3-day treatment schedule (short treatment) and a 6-day treatment schedule (long treatment).

After 3 days of therapy (Table 2, short treatment) vancomycin (30 mg/kg q12h) showed no appreciable effect, while daptomycin q12h significantly reduced the level of valvular infection ($P < 10^{-3}$). Similarly, after 6 days of therapy (Table 2, long treatment), the density of MSSA2 recovered from the valvular homogenates after vancomycin treatment (30 mg/kg q12h) was only slightly diminished when compared with bacterial density at the start of treatment. However, increasing the number of injections of vancomycin from two to four per day appreciably reduced the level of valvular infection compared with that in control rats ($P < 10^{-3}$). However, such a q6h dosing schedule was not sufficient to achieve an efficacy similar to that of daptomycin at 10 mg/kg q12h ($P < 10^{-2}$).

When decreasing doses and schedules of daptomycin treatment were tested, with the exception of daptomycin at 5 mg/kg q24h, which clearly failed to cure infected valves, all regimens (including daptomycin at 5 mg/kg q12h and daptomycin at 10 mg/kg q24h) were highly effective in reducing both the incidence and the magnitude of infection due to strain MSSA2. These regimens were as effective as vancomycin at 30 mg/kg q6h.

Finally, cloxacillin treatment for 6 days significantly reduced the number of bacteria when compared with controls ($P < 10^{-4}$).

The results of studies of the efficacies against endocarditis of the various treatments started 15 h after infection induced by strain MRSA3 are shown in Table 3. As can be seen, after 3 days of therapy, the treatment regimen consisting of vancomycin at 30 mg/kg q12h failed to reduce bacterial counts, while the regimen consisting of daptomycin at 10 mg/kg q12h already showed a significant efficacy ($P < 10^{-3}$). After 6 days of therapy, two of the daptomycin treatment regimens (10 mg/kg q24h and 10 mg/kg q12h) showed efficacies similar to that of the 30-mg/kg q6h vancomycin regimen.

In addition to the late treatment with high valvular counts, vancomycin (30 mg/kg q12h) was also given for 3 days to rats 8 h after challenge with strain MRSA3, when the bacterial counts were lower (7.5 $\log_{10}$CFU/g), resulting in 40% of the vegetations being sterile compared with 0% when the same treatment was started after 15 h.

The MICs for representative strains recovered from rats still infected after therapy with vancomycin, daptomycin, and cloxacillin were similar to those for the bacterial inoculum used for challenge.

DISCUSSION

The purpose of the present study was to evaluate in a rat model of endocarditis the in vivo efficacy of the new antibi-

otic daptomycin for the treatment of *S. aureus* infections and to compare it with those of known antistaphylococcal antibiotics.

When the treatment was started early (8 h) after infection (MSSA strains), the level of valvular infection was only 10^6 CFU/g of vegetation, and 3 days of therapy was equally effective with all antibiotic regimens tested. Thus, in order to discriminate between the different treatment regimens, two modifications of the experimental protocol were introduced when strain MSSA2 as well as strain MRSA3 was tested. First, a longer time interval was allowed between the intravenous inoculation of the test strain and the beginning of treatment, so that higher bacterial counts could develop on the valves (i.e., 10^8 to 10^9 CFU/g of vegetation, instead of 10^6 CFU/g). Second, the duration of antibiotic administration was extended from 3 to 6 days. When this modified protocol was used, significant differences became apparent both when the efficacies of identical treatment regimens tested in the two experimental conditions were compared and when the various treatment regimens were compared. Indeed, while vancomycin, cloxacillin, and daptomycin were highly and equally effective against the MSSA strains after 3 days of treatment of low-bacterial-count endocarditis, the efficacies of all three antibiotics diminished when tested for the treatment of high-bacterial-count endocarditis (strain MSSA2). This difference was most pronounced for the vancomycin and cloxacillin regimens, which were already very active after 3 days of treatment in low-bacterial-count endocarditis but did not reach a similar efficacy even after 6 days of treatment in high-bacterial-count endocarditis.

A similarly decreased efficacy in the treatment of bacterial endocarditis with increasing bacterial counts in vegetations has been reported for rabbits by Enzler and colleagues for the treatment of *Streptococcus bovis* endocarditis (M. J. Enzler, M. S. Rouse, N. K. Henry, and W. R. Wilson, 25th ICAAC, abstr. no. 470, 1985) and by Sullam et al. for enterococcal endocarditis (11).

Thus, these observations underscore the crucial role of clearly defining the experimental conditions when comparing the efficacies of various antibiotics in the treatment of experimental endocarditis and stress the need for testing various experimental conditions when establishing the respective values of various antibiotic regimens.

When the most stringent test conditions of high-bacterial-count endocarditis were used, daptomycin appeared more active than vancomycin and cloxacillin against MSSA2 endocarditis after both 3 and 6 days of treatment and more active than vancomycin against MRSA3 endocarditis after 3 days of treatment (both drugs were equally effective after 6 days of treatment).

Recently, daptomycin administered intravenously to rabbits for the treatment of MRSA endocarditis as a single daily dose of 10 mg/kg was as effective after 4 days as vancomycin given at a dosage of 25 mg/kg twice a day (7).

Since the in vivo efficacy of daptomycin against various pathogens is not fully established yet, and since the doses and levels in blood of this compound are not yet defined, we attempted to establish a dose-response relationship for the treatment of both MSSA and MRSA endocarditis. We took advantage in this study of the fact that daptomycin has a prolonged half-life in rats, allowing a q24h or q12h schedule. Against both the MSSA and MRSA strains, daptomycin displayed in vivo a dose-related efficacy. In the MSSA2 experiments, daptomycin administered at a dosage of 10 mg/kg q12h gave significantly better results than 5 mg/kg q12h, whereas 5 mg/kg q24h was not effective. In the MRSA3 experiments, a dose-related efficacy was also observed with daptomycin, but the doses required to cure infection were higher than that required to cure MSSA endocarditis. This in vivo dose-related efficacy paralleled the in vitro time kill experiments performed with daptomycin. Indeed, as previously observed by others (4, 10, 12), and particularly during the early phase (12), we observed a striking dose-dependent early bactericidal activity of daptomycin in vitro, particularly for the MSSA strains. Indeed, at the high concentrations tested (25 and 60 μg/ml, corresponding to peak concentrations in serum after one injection of 5 or 10 mg/kg, respectively), daptomycin was rapidly bactericidal (within 6 and 4 h, respectively), whereas at lower concentrations (0.5 and 2.5 μg/ml, corresponding to 2 and 10 times the MIC), daptomycin was only bacteriostatic. In contrast, such a dose-dependent bactericidal effect was not observed with vancomycin, which displayed in vitro only a slow bactericidal effect independent of the concentration of antibiotic used and never achieved sterility in test tubes. Thus, for both MSSA and MRSA strains, the in vivo dose-dependent efficacy displayed by daptomycin could be related to an increased bactericidal activity that paralleled increased doses and shorter intervals of administration, a phenomenon that might influence the choice of drug regimens in clinical use.

In conclusion, considering its pharmacokinetic properties, its good in vitro activity associated with its rapid bactericidal effect at high concentrations, and its excellent efficacy against MSSA and MRSA endocarditis in rats, daptomycin appears to be a potent agent against infections due to gram-positive cocci, particularly MRSA.

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