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Teicoplanin Alone or Combined with Rifampin Compared with Vancomycin for Prophylaxis and Treatment of Experimental Foreign Body Infection by Methicillin-Resistant *Staphylococcus aureus*

HEINZ J. SCHAAD,† CHRISTIAN CHUARD,‡ PIERRE VAUDAUX,* FRANCIS A. WALDVOGEL, AND DANIEL P. LEW

Division of Infectious Diseases, University Hospital, CH-1211 Geneva 14, Switzerland

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The prophylactic and therapeutic activities of teicoplanin were evaluated in two different experimental models of foreign body infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). In a guinea pig model of prophylaxis, subcutaneously implanted tissue cages were infected at a >90% rate by 10^2 CFU of MRSA in control animals. A single dose of 30 mg of teicoplanin per kg of body weight administered intraperitoneally 6 h before bacterial challenge was as effective as vancomycin in preventing experimental infection in tissue cages injected with either 10^2, 10^3, or 10^4 CFU of MRSA. In a rat model evaluating the therapy of chronic tissue cage infection caused by MRSA, the efficacy of a 7-day high-dose (30 mg/kg once daily) regimen of teicoplanin was compared with that of vancomycin (50 mg/kg twice daily). Whereas high levels of teicoplanin were found in tissue cage fluid, continuously exceeding its MBC for MRSA by 8- to 16-fold, no significant reduction in the viable counts of MRSA occurred during therapy. In contrast, either vancomycin alone or a combined regimen of high-dose teicoplanin plus rifampin (25 mg/kg twice daily) could significantly decrease the viable counts in tissue cage fluids. Whereas the bacteria recovered from tissue cage fluids during therapy showed no evidence of teicoplanin resistance, they failed to be killed even by high levels of this antimicrobial agent. The altered susceptibility of in vivo growing bacteria to teicoplanin killing might in part explain the defective activity of this antimicrobial agent when used as monotherapy against chronic *S. aureus* infections. These data may indicate the need for a combined regimen of teicoplanin with other agents such as rifampin to optimize the therapy of severe staphylococcal infections.

Bacterial infections of prosthetic devices are a major cause of morbidity and implant failure. Antimicrobial therapy of foreign body infections caused by *Staphylococcus aureus* is notoriously difficult, and microbial eradication frequently requires the removal of infected materials. An additional serious problem for the therapy of foreign body infections is the increasing incidence of methicillin-resistant strains of *S. aureus* (MRSA) that frequently express a large number of additional determinants for resistance to several major categories of antistaphylococcal agents. Although vancomycin is the reference antibiotic for treating MRSA infections, its activity against deep-seated infections is not always optimal (30, 32) and frequently requires the parallel administration of other antimicrobial agents such as aminoglycosides or rifampin (18, 49).

There are three major concerns about increasing the use of vancomycin. The first one is its narrow toxic to therapeutic ratio involving serious toxic side effects; the second one is the exclusive intravenous route for administration of this agent, thus involving extensive hospital stay and costs; the third one is the growing concern about the possible acquisition of vancomycin resistance by staphylococci (27), which would result in a major clinical and epidemiological problem.

Teicoplanin is a glycopeptide antibiotic with an antibacterial spectrum similar to that of vancomycin (24), but with a much longer half-life and less serious side effects (16, 23, 43, 52). Unlike vancomycin, teicoplanin is well tolerated after intramuscular administration, and its prolonged half-life is suitable for once-daily dosing (43). Several clinical or experimental studies evaluated the efficacy of teicoplanin for treating deep-seated staphylococcal infections. Taken together, these different studies have led to discrepant results and controversial interpretations concerning teicoplanin safety and efficacy (see reviews in references 8, 15, and 16). The divergent results of these clinical studies may be explained by significant differences in their design, for example, the choice of open (4, 22, 23, 31, 33, 36, 47) versus comparative (7, 17, 20, 46, 48, 50) trials, and by the wide range of dosage regimens, treatment durations, and antibiotic combinations used by the different investigators.

The major objective of our experimental study was to evaluate the efficacy of teicoplanin in two related animal models of foreign body infections caused by an MRSA strain (12, 34). The first of these models (5) was more suitable for assessing the prophylactic activity of teicoplanin on MRSA challenge, whereas the second one (34) evaluated its activity for the treatment of chronic subcutaneous implant-related infections caused by MRSA. In both animal models, teicoplanin was administered as a high-dose regimen to overcome the potential antagonistic effect of high levels of protein binding by plasma or tissue cage fluid components (2, 10, 25, 29).

* Corresponding author. Mailing address: Division of Infectious Diseases, University Hospital, 1211 Geneva 14, Switzerland. Phone: (4122) 37 29 826. Fax: (4122) 37 29 830.

† Present address: Division of Clinical Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21287.

‡ Present address: Laboratory of Clinical Microbiology, Duke University Medical Center, Durham, NC 27710.

(The results of this study were presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy [44].)

MATERIALS AND METHODS

Bacterial strains. MRSA MRGR3 (12, 34) was used in both animal models. In addition, methicillin-susceptible (13, 14, 45) *S. aureus* (MSSA) I20 was also used for some animal studies in the chronic infection model. Both strains were isolated from patients with catheter-related sepsis and were selected for their virulence properties in the animal models of foreign body infections. Strain MRGR3 is heterogeneously resistant to methicillin and has additional determinants for resistance to penicillin, gentamicin, chloramphenicol, erythromycin, tetracycline, and polymyxin B.

Antimicrobial agents. For the in vitro studies, the following laboratory standards with known potencies were supplied by the indicated manufacturers: teicoplanin by Lepetit Research Center (Varese, Italy), vancomycin hydrochloride by Laboratory Lilly (Giessen, Germany), and rifampin by Laboratory Ciba-Geigy (Basel, Switzerland). For animal studies, teicoplanin (Targocid, Merell Dow, Horgen, Switzerland), vancomycin (Lilly), and rifampin (Ciba-Geigy) were dissolved in solvents as recommended by their manufacturers.

A single lot of Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) with a low content of Ca^{2+} (16 μg/ml) and Mg^{2+} (7 μg/ml) was used. For all in vitro tests, the Mueller-Hinton broth was supplemented (SMHB) with 50 μg of Ca^{2+} per ml and 25 μg of Mg^{2+} per ml.

In vitro studies. The MICs of each agent for MRSA MRGR3 were determined by a macrodilution method by using SMHB as indicated above and a standard inoculum of 10^6 CFU/ml (37). To screen for the possible carryover effects of each antibiotic during the MBC determinations, 100-μl portions were taken from all tubes with no visible growth. These were subcultured, either undiluted or diluted 10-fold in saline, on Mueller-Hinton agar for 36 h at 37°C. The MBC was defined as the lowest concentration that killed 99.9% of the original inoculum.

To evaluate how protein binding altered the in vitro antimicrobial activity of teicoplanin (2, 10, 25), the MICs and MBCs of this glycopeptide for *S. aureus* were determined in a 2-ml volume containing a mixture of SMHB and pooled tissue cage fluid in a 1:1 ratio.

To evaluate the susceptibility to teicoplanin of *S. aureus* recovered from infected tissue cage fluids, bacteria were isolated from cage fluids by centrifugation and were treated with 0.1% Triton X-100 and sonication to disrupt the host cells as described previously in detail (13). Previously described control experiments demonstrated that this procedure, which is used to reduce bacterial clumping, was harmless for ex vivo bacteria regarding their ability to multiply and their susceptibility to antibiotics (13). The MICs and MBCs of teicoplanin for the bacteria tested directly from tissue cage samples were determined as described above with organisms grown in vitro. To make the comparison with ex vivo bacteria more relevant (13), bacteria grown in vitro were taken from stationary-phase cultures.

Killing kinetic studies. Initial time-kill studies were performed with exponential-phase bacteria by using standard assay conditions (38). Glass tubes containing 10 ml of SMHB with either 5 μg of vancomycin per ml or 20 μg of teicoplanin per ml either alone or combined with 0.5 μg of rifampin per ml were incubated with 10^6 CFU of *S. aureus* per ml in a shaking water bath at 37°C. The number of viable organisms was determined by subculturing 50 μl of 10-fold serially diluted portions of broth on Mueller-Hinton agar (Difco) after 0, 2, 4, 6, and 24 h of incubation. Bacteria were plated with a spiral plater (Spiral System, Cincinnati, Ohio), and the colonies were counted with a laser colony counter (Spiral) after 24 h of incubation at 37°C. The detection limit was 2 $\log_{10}$ CFU/ml with all antibiotics tested. No significant carryover of antibiotics was observed by using these experimental conditions (13, 34).

To compare the elimination rate of *S. aureus* recovered from tissue cage fluids with that of the same strain grown in vitro, tissue cage bacteria isolated as described above were directly exposed to 16 μg of teicoplanin per ml in tubes containing 2 ml of either SMHB or a 1:1 ratio of SMHB and tissue cage fluid. To make the comparison with ex vivo bacteria more relevant (13), bacteria grown in vitro were taken from stationary-phase cultures.

Prophylaxis of tissue cage infections. Four polytetrafluoroethylene (Teflon) multiperforated tissue cages each containing three polymethylmethacrylate (PMMA) coverslips (7 by 7 mm) were implanted subcutaneously in guinea pigs under aseptic conditions as described previously in detail (5, 54). At 3 weeks after implantation, tissue cage fluids were aseptically aspirated and were checked for sterility. Then, tissue cages were inoculated with 0.1 ml of saline containing 10^2, 10^3, or 10^4 CFU of MRSA MRGR3, as routinely checked by plating on Mueller-Hinton agar. Experimental infection was confirmed by quantitatively culturing aspirated tissue cage fluid (5, 54).

To study the prevention of experimental infection by the antimicrobial agents, a single dose of either vancomycin or teicoplanin (30 mg/kg of body weight) was administered intraperitoneally 3 or 6 h, respectively, before the inoculation of live staphylococci into the tissue cages. This lag time was necessary to obtain peak levels of either antimicrobial agent in tissue cage fluid at the time of bacterial inoculation. At 24 h, 48 h, and 7 days after the injection of 10^2, 10^3, or 10^4 CFU of MRSA MRGR3, quantitative cultures were performed by plating 100 μl of tissue cage fluid, either undiluted or serially diluted 10-fold on Mueller-Hinton agar. Because of the small volume (100 μl) of tissue cage fluid which could be aspirated during repeated punctures, samples yielding no single organism were scored as containing <10 CFU/ml. At day 7 the cages were removed and the coverslips were cultured in Mueller-Hinton broth at 37°C for 7 days. A brief sonication (60 W, 1 min) was performed to disrupt the biofilm and phagocytic cells in order to optimize the yield of viable bacteria. The detection limit was 1 CFU per coverslip. The efficacy of teicoplanin in yielding culture-negative fluids and coverslips in tissue cages challenged by identical numbers of inoculated organisms was compared with that of vancomycin by Fisher's two-tailed (2-by-2) exact test.

Treatment of chronic tissue cage infections. Four tissue cages each containing three PMMA coverslips (7 by 7 mm) were implanted subcutaneously in Wistar rats as described previously (34). At 3 weeks after implantation, tissue cage fluid was aspirated and was checked for sterility. To establish a chronic local infection by MRSA, tissue cages were inoculated with 0.1 ml of saline containing 0.2×10^6 to 2×10^6 CFU of stationary-phase organisms of strain MRGR3 as described previously (12, 34). A similar protocol was used for MSSA I20 (45). Three weeks later, all tissue cages containing more than 10^5 CFU/ml of fluid were included in the therapeutic protocols.

Rats infected with MRSA MRGR3 were randomized to receive (by the intraperitoneal route for 7 days) either teicoplanin (30 mg/kg once a day), teicoplanin (30 mg/kg once a

day) and rifampin (25 mg/kg twice a day), or vancomycin (50 mg/kg twice a day) or were left untreated. Rats infected with MSSA were treated with identical regimens of teicoplanin alone, teicoplanin plus rifampin, and vancomycin. An additional group received oxacillin (200 mg/kg twice a day) for 7 days.

At 12 h after the last injection of antibiotic(s), quantitative cultures of 10-fold serially diluted tissue cage fluid were performed on Mueller-Hinton agar. Possible bacterial clumps were disrupted by sonication for 1 min at 60 W (Branson 2200; Branson Ultrasonics, Danbury, Conn.) before plating. Quantitative bacterial counts were determined with a detection limit of 100 CFU/ml and are expressed as $\log_{10}$ CFU per milliliter. For each cage, the differences between CFU counts from day 1 and day 8 were determined and expressed as delta $\log_{10}$ CFU/ml. For each treatment group, results were expressed as means ± standard errors of the means. Comparison of bacterial counts in the different groups was performed by one-way analysis of variance and Newman-Keuls multiple comparisons procedure. Data were considered significant when P was <0.05 by using two-tailed significance levels.

Resistance to antimicrobial agents. The bacteria recovered from cage fluids or coverslips on day 8 were screened for the emergence of resistance to rifampin or teicoplanin: 100-μl samples of 10-fold-diluted cage fluid or sonicated coverslips were plated onto Mueller-Hinton agar containing either 1 μg of rifampin per ml or 10 μg of teicoplanin per ml. In some experiments, resistance to teicoplanin was screened on Mueller-Hinton agar containing lower concentrations (4 or 8 μg/ml) of antimicrobial agent. Plates were incubated for 48 h at 37°C. The detection limits were 2 and 1 $\log_{10}$ CFU/ml for tissue cage fluids and coverslips, respectively.

Pharmacokinetics of antimicrobial agents. The pharmacokinetic properties of vancomycin in guinea pig tissue cage fluid (5) or of vancomycin, rifampin, and oxacillin in rat tissue cage fluid have been estimated previously (34, 45). The concentrations of teicoplanin in serum and tissue cage fluid were determined by fluorescence polarization immunoassay (TDx; Abbott Laboratories, Chicago, Ill.), which was kindly performed by M. Schmidt (Laboratoire Central de Chimie Clinique, Hôpital Cantonal Universitaire, Geneva, Switzerland). In guinea pigs, the concentrations of teicoplanin were measured in tissue cage fluid at various time intervals (1, 2, 4, 6, 8, 12, and 24 h) after intraperitoneal administration of a single dose of 30 mg of antimicrobial agent per kg. In rats treated once a day with a 30-mg/kg regimen of teicoplanin, the pharmacokinetics of the antimicrobial agent in both serum and tissue cage fluids were determined at similar time intervals on day 4 (to allow equilibrium concentrations for teicoplanin) and day 7 of therapy.

RESULTS

In vitro studies. The MICs and MBCs of teicoplanin, vancomycin, and rifampin for MRSA MRGR3 were 1 and 2, 1 and 2, and 0.01 and 0.02 μg/ml, respectively.

Time-kill studies showed the rapid elimination of exponential-phase cultures of MRSA grown in vitro by teicoplanin or vancomycin. The reduction in viable counts exceeded 3 $\log_{10}$ CFU/ml after 6 h (Fig. 1). The addition of rifampin to the teicoplanin regimen strongly antagonized its in vitro bactericidal activity, since the decrease in viable counts of MRSA was <1.6 $\log_{10}$ at 24 h (Fig. 1).

Prophylaxis of tissue cage infection. In untreated animals, 15 of 16 tissue cages challenged with 10^2 CFU of MRSA MRGR3 developed infection, with bacterial counts exceeding

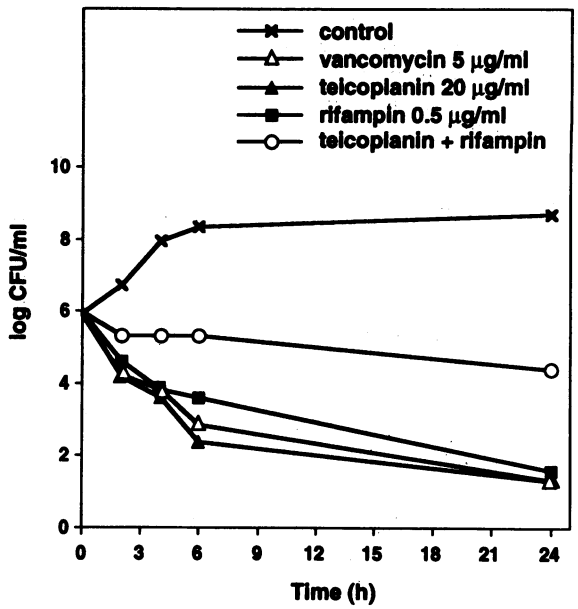

FIG. 1. Rate of in vitro elimination of exponential-phase cultures of *S. aureus* MRGR3 grown in SMHB by either vancomycin (5 μg/ml), teicoplanin (20 μg/ml), rifampin (0.5 μg/ml), or teicoplanin (20 μg/ml) plus rifampin (0.5 μg/ml).

10^4 CFU/ml of fluid at 24 h and later. With higher bacterial inocula, the infection rate was 100%. These rates of tissue cage infection by various inocula of MRSA MRGR3 in guinea pigs were similar to those recorded previously with MSSA Wood 46 (5, 54).

The mean concentrations of teicoplanin in the tissue cage fluid of guinea pigs at various time intervals after administration are shown in Fig. 2A. The levels of teicoplanin in tissue cage fluid slowly increased up to 6 h, reaching plateau values averaging 18 μg/ml from 6 to 12 h and slowly declining thereafter. Thus, a single prophylactic dose of teicoplanin produced bactericidal levels (four to eight times the MBC) in tissue cage fluid for the next 24-h period. In comparison, the mean concentrations of vancomycin in tissue cage fluid determined in a previous study (5) were 7.1, 12.2, and 2.0 μg/ml at 3, 6, and 24 h, respectively. These comparative pharmacokinetic data of teicoplanin and vancomycin indicated optimal lag times between drug administration and bacterial challenge of 6 h for teicoplanin and 3 h for vancomycin.

Table 1 shows that teicoplanin reduced colony counts below the detection limit of 10 CFU/ml of tissue cage fluid within 48 h in all cages challenged with either 10^2 ($n = 9$), 10^3 ($n = 9$), or 10^4 ($n = 9$) CFU of MRSA MRGR3. At 7 days, however, some of the tissue cages challenged with either 10^3 or 10^4 CFU of MRSA showed evidence of bacterial regrowth (Table 1). Whereas vancomycin-treated animals showed transient differences from teicoplanin-treated animals at 48 h, since only 88 and 44% of the tissue cages challenged with 10^3 and 10^4 CFU, respectively, were culture negative at that time, equivalent protection rates were reached in both treatment groups when protection rates were scored at 7 days (Table 1). Furthermore, coverslips from culture-negative tissue cage fluids cultured at 7 days were all found to be sterile (limit of detection, 1 CFU/ml).

Treatment of chronic tissue cage infections. The average concentrations of teicoplanin in rat serum, assayed at day 4 of therapy, peaked at 126 μg/ml at 2 h after administration of a 30-mg/kg daily dose. The half-life of teicoplanin elimination in

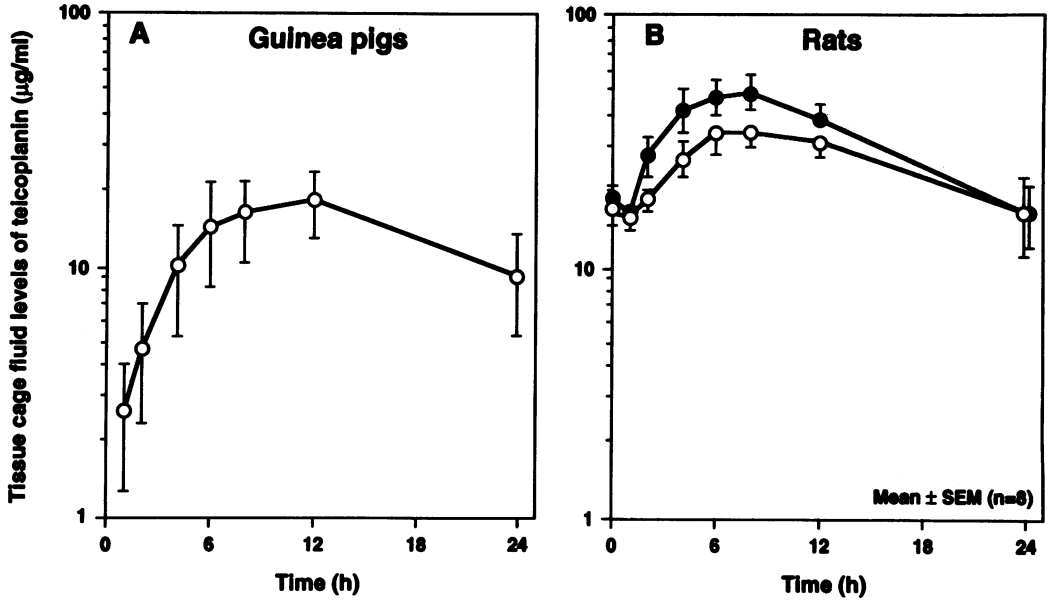

FIG. 2. Levels of teicoplanin in tissue cage fluid of guinea pigs that received a single 30-mg/kg dose of antimicrobial agent (A) or rats on day 4 of once-a-day therapy with either 30 mg of teicoplanin per kg alone (○) or teicoplanin plus rifampin (25 mg/kg twice a day) (●) (B).

serum was approximately 6 h, and bactericidal levels of 12 μg/ml were still present at 24 h. In tissue cage fluid, teicoplanin levels showed a slow and continuous increase up to 8 h, reaching a plateau of 35 μg/ml and a residual level of 17 μg/ml at 24 h (Fig. 2B). Equivalent levels of drug in tissue cage fluid were recorded on day 4 and day 7 (data not shown), thus indicating the absence of significant drug accumulation during therapy. Concomitant administration of rifampin (25 mg/kg twice a day) produced a significant increase in the concentrations of teicoplanin in the sera and tissue cage fluids of treated rats (Fig. 2B). Average peak and trough levels of vancomycin in tissue cage fluid were 12 and 2 μg/ml at 4 and 12 h, respectively, as described previously (34). Average peak and trough levels of oxacillin in tissue cage fluid were 45 and 5.7 μg/ml at 2 and 12 h, respectively, as described previously (45).

Of 159 cages infected with MRSA MRGR3, 26 were excluded because of inadequate low bacterial counts and 32 were excluded because of spontaneous shedding from animals during therapy. At the onset of therapy, bacterial counts for the remaining 101 tissue cages were 6.44 ± 0.22 $\log_{10}$ CFU/ml for controls (n = 19), 6.22 ± 0.16 $\log_{10}$ CFU/ml for animals receiving teicoplanin (n = 31), 6.56 ± 0.25 $\log_{10}$ CFU/ml for animals receiving vancomycin (n = 16), and 6.42 ± 0.17 $\log_{10}$ CFU/ml for animals receiving teicoplanin and rifampin (n = 35). At the end of the 7-day treatment period, bacterial counts in the tissue cages (n = 19) of control animals showed a slight and nonsignificant increase of 0.38 ± 0.20 $\log_{10}$ CFU/ml. The high-dose regimen of teicoplanin was ineffective (Fig. 3), since the viable counts of MRSA increased by 0.65 ± 0.17 $\log_{10}$ CFU/ml in tissue cage fluids (n = 31). In contrast, the vancomycin regimen led to a significant reduction in the

TABLE 1. Comparison of teicoplanin and vancomycin in the prophylactic treatment of tissue cage infections caused by *S. aureus* MRGR3

Antibiotic[a]	No. of CFU of *S. aureus* inoculated	No. of negative tissue cage[b]/no. analyzed (%) after:	
		48 h	7 days[c]
None (control)	10^2	1/16 (6)	1/16 (6)
Teicoplanin	10^2	9/9 (100)	9/9 (100)
	10^3	9/9 (100)	8/9 (89)
	10^4	9/9[c] (100)	6/9 (67)
Vancomycin	10^2	7/7 (100)	6/7 (86)
	10^3	7/8 (88)	7/8 (88)
	10^4	4/9[d] (44)	4/9 (44)

[a] Teicoplanin and vancomycin were both given at a dose of 30 mg/kg.
[b] Culture-negative samples (100 μl) of tissue cage fluid were scored as <10 CFU/ml, which was the lower limit of detection.
[c] Identical results were obtained for coverslips and tissue cage fluids.
[d] $P < 0.05$ for teicoplanin versus vancomycin.

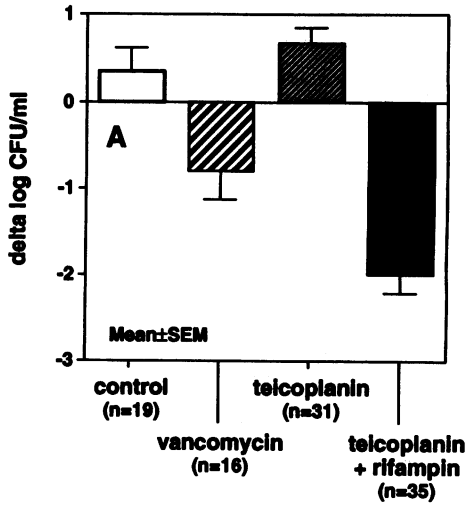

FIG. 3. Decrease in viable counts of *S. aureus* MRGR3 in tissue cage fluids of rats treated with the different regimens for 7 days.

bacterial counts in tissue cage fluids of 0.78 ± 0.34 $\log_{10}$ CFU/ml in comparison with the reductions in tissue cage fluids from controls and teicoplanin-treated animals ($P < 0.01$). Finally, the most efficient treatment regimen was the combination of teicoplanin and rifampin, which led to a significant ($P < 0.01$ versus all other regimens) reduction of 2.00 ± 0.21 $\log_{10}$ CFU/ml of tissue cage fluids ($n = 35$) (Fig. 3).

The effectivenesses of teicoplanin (alone or with rifampin), oxacillin, and vancomycin against chronic tissue cage infections caused by MSSA I20 were also compared; the properties of strain I20 have been described previously (13, 14, 45). Whereas at the end of the 7-day treatment period no regimen with any single agent led to any statistically significant decrease in viable counts in tissue cage fluids compared with that in controls, combined therapy with high-dose teicoplanin and rifampin was significantly ($P < 0.01$) more effective than the monotherapies in decreasing the viable counts in tissue cage fluids by 2.17 ± 0.23 $\log_{10}$ CFU/ml ($n = 19$).

Activity of teicoplanin on bacteria grown in vitro and in vivo. The lack of efficacy of the high-dose teicoplanin monotherapy against chronic tissue cage infection caused by *S. aureus* might result either from extensive protein binding, decreasing the free drug level, or from a major change in the susceptibility of the bacterial population growing in tissue cage fluid to antibiotic killing, or from the combined effects of these factors. The MICs and MBCs of teicoplanin for bacteria grown in vitro in either the logarithmic or the stationary phase were identical (1 μg/ml) and were moderately affected by the presence of proteins in the medium. In SMBH supplemented with 50% tissue cage fluid, the average increase in MICs and MBCs was twofold for exponentially growing organisms and fourfold for stationary-phase organisms.

Susceptibility tests were also performed with bacteria recovered from tissue cage fluid before and after therapy. The MICs (1 μg/ml) of teicoplanin for bacteria recovered from tissue cages in SMHB were similar to those of organisms grown in vitro and did not change during therapy. In contrast, the MBCs (>32 μg/ml) of teicoplanin for both pre- and posttherapy organisms were markedly elevated over those for bacteria grown in vitro. These elevated MBCs against bacteria recovered from tissue cage fluid were due to their incomplete elimination by concentrations ranging from 1 to 16 μg/ml. The elevated MBC-to-MIC ratio of teicoplanin against bacteria recovered from tissue cages reproduced previous findings showing the increased tolerance of tissue cage fluid organisms to various antibiotics including vancomycin (13). Since these effects were observed in the absence of any tissue cage fluid components added to SMHB, they indicated that susceptibility changes rather than interference with the teicoplanin bactericidal activity by protein binding occurred in the population of bacteria in tissue cage fluid.

To further explore the defective bactericidal activity of teicoplanin against tissue cage fluid organisms of strain MRGR3 at concentrations relevant to therapy, time-kill studies were performed. Figure 4 shows the lack of significant elimination by 16 μg of teicoplanin per ml of bacteria recovered from tissue cage fluid after therapy, with average decreases in viable counts of 0.4 and 1 $\log_{10}$ CFU/ml at 6 and 24 h, respectively. The very low elimination rate of tissue cage bacteria contrasted with the faster rate of elimination of bacteria in the stationary phase grown in vitro tested in parallel (Fig. 4). Such differences between organisms recovered from tissue cages and in vitro were independent of the presence or absence of 50% tissue cage fluid added to SMHB (Fig. 4), thus ruling out any significant contribution of protein binding to the altered susceptibility of tissue cage bacteria. Furthermore, the

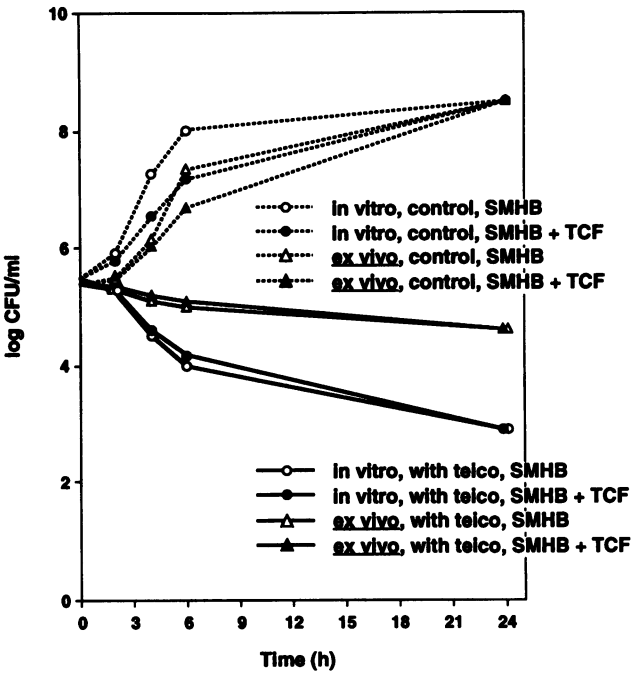

FIG. 4. Killing kinetic studies of *S. aureus* MRGR3 with teicoplanin (teico; 16 μg/ml). Bacteria grown in vitro to the stationary phase were tested, as were those recovered from pooled, chronically infected tissue cage fluids. Incubation was done in either SMHB or a 1:1 mixture of SMHB and sterile tissue cage fluids (TCF) pooled from rats.

resistance of bacteria recovered from tissue cages to killing by teicoplanin was already observed with organisms tested before therapy. In four additional experiments in which tissue cage fluid bacteria were analyzed before any antibiotic treatment, the elimination rates of these organisms ranged from 0.37 to 0.53 and 0.96 to 1.06 $\log_{10}$ CFU/ml at 6 and 24 h, respectively. In two of these experiments, the decrease in the viable counts of tissue cage bacteria by 8 μg of vancomycin per ml was tested in parallel and averaged 0.85 and 2.0 $\log_{10}$ CFU/ml at 6 and 24 h, respectively.

Screening of teicoplanin resistance during therapy. In initial studies, teicoplanin resistance was screened by direct plating of tissue cage fluid bacteria on agar containing 10 μg of teicoplanin per ml. Bacterial suspensions from 14 of 31 (45%) tissue cage fluid samples tested at the end of teicoplanin monotherapy yielded organisms growing on teicoplanin-supplemented agar. The proportion of organisms growing in the presence of 10-fold the MIC of teicoplanin was quite constant from cage to cage, averaging 4×10^{-4}. However, the ability to grow on teicoplanin-enriched agar was unstable and was limited to bacteria directly tested from infected tissue cage fluids. After transfer, all colonies previously grown on teicoplanin-containing agar expressed normal susceptibility to teicoplanin (MIC, 1 μg/ml). Further studies documented that even ex vivo bacteria from untreated animals or from those tested before therapy contained an increased proportion (3×10^{-5}) of organisms growing on agar containing 10 μg of teicoplanin per ml (44). This proportion was much higher than the low frequency ($<10^{-9}$) of organisms of strain MRGR3 grown in vitro. To determine whether the increased tendency of tissue cage fluid bacteria to grow on teicoplanin-enriched agar represented a first step toward the emergence of teico-

planin resistance, we sequentially tested bacteria removed from tissue cages before and after teicoplanin monotherapy and evaluated the proportion of colonies growing on agar containing either four- or eightfold the MICs of teicoplanin. The proportions of organisms growing on 4 and 8 μg of teicoplanin per ml were 7.7×10^{-5} and 1.9×10^{-5} before therapy and 5.9×10^{-5} and 1.0×10^{-5} after therapy, respectively. This absence of any significant increase in the frequency of resistant colonies during therapy ruled out support for the possibility of the emergence of a resistant subpopulation promoted by the high-dose teicoplanin regimen.

Emergence of resistance during combined therapy. The potential emergence of bacteria resistant to rifampin or teicoplanin during combined therapy was also studied. No rifampin- or teicoplanin-resistant organism of MRSA MRGR3 was found in the fluids or on coverslips of 35 tissue cages from animals treated with teicoplanin and rifampin. Similar data (data not shown) were found with MSSA I20.

DISCUSSION

The optimal dosing of teicoplanin required for the safe and effective treatment of serious staphylococcal infections has frequently been discussed and reevaluated (53) since early clinical studies with maintenance doses of 200 mg of teicoplanin reported success rates of <50% for the therapy of staphylococcal bacteremia, endocarditis, and osteomyelitis (7, 8, 15, 22). Subsequent results from a number of additional open or comparative trials performed over the past decade (4, 17, 20, 23, 31, 33, 36, 46–48, 50) combined with more accurate pharmacokinetic and protein binding estimates (2, 10, 29, 43) have led to recommendations (15, 23) of higher daily doses of teicoplanin, ranging from 6 (15) to 12 (53) or 15 (23) mg/kg/day. With the 15-mg/kg teicoplanin regimen, very high levels of drug in serum (>30 μg/ml), equivalent to 30 times the MICs of teicoplanin for susceptible isolates of *S. aureus*, were continuously present in patients (23) and could overcome protein binding by serum components.

Teicoplanin was also evaluated in various animal models (1, 9–11, 19, 28, 29, 39, 41, 51), which generally showed that this glycopeptide has activity equivalent to that of vancomycin for the therapy of experimental endocarditis caused by either *S. aureus* (1, 11) or *Staphylococcus epidermidis* (19), except when the emergence of teicoplanin resistance led to therapeutic failure (28, 29). A single animal study systematically explored pharmacokinetic parameters that would optimize the efficacy of teicoplanin therapy for *S. aureus* endocarditis (10). Despite a wide range of experimental conditions, including high-dose and low-dose regimens and various routes of administration (10), no simple relationship could be established between dosage, levels of drug in serum, and the therapeutic efficacy of teicoplanin.

To avoid interference by protein binding (2, 10, 29, 43) in the evaluation of teicoplanin activity for either the prophylaxis or the treatment of chronic *S. aureus* infection, we selected a high-dose regimen of 30 mg/kg administered as a single dose to guinea pigs or as multiple doses to rats. Under this regimen, teicoplanin reached trough levels of 16 μg/ml in rat tissue cage fluid, which is equivalent to 8- to 16-fold its MBC for MRSA. Control experiments assessed that protein binding by tissue cage fluid components did not interfere with the bactericidal activity of teicoplanin, at least when this activity was evaluated against organisms grown in vitro at a concentration equivalent to the trough level in tissue cage fluid. In contrast to cultures of strain MRGR3 grown in vitro, tissue cage fluid bacteria were not killed to a significant extent by 16-fold the MIC of teicoplanin, irrespective of the presence or absence of tissue cage fluid components. There was also some significant difference in the in vivo activity of teicoplanin, which proved significant in the guinea pig prophylactic model of foreign body infection and which contrasted with the lack of activity in the rat model of chronic infection. This might be due to the fact that in the prophylactic model, the bacterial populations injected into tissue cages and immediately exposed to high levels of antibiotic are in metabolic conditions similar to those expressed during their growth in vitro. In contrast, chronically infected tissue cages might contain a much lower proportion of actively multiplying organisms. It is striking to notice the significantly better activity of teicoplanin in experimental models of *S. aureus* endocarditis (1, 10, 11, 28, 29) than in chronic models of osteomyelitis (39) or tissue cage infections. Treatment protocols for rabbit endocarditis caused by *S. aureus* are generally started within 24 h after infection, namely, just after the rapid growth of the microbial population within the infected vegetations. In contrast, the lack of efficacy of teicoplanin monotherapy against chronic osteomyelitis was related to the altered metabolic conditions of *S. aureus* prevailing in the anaerobic environment in the osteomyelitic rat bone (39), leading to a 16-fold increase in the MIC of teicoplanin for *S. aureus* (39).

Previous observations made in various laboratories (6, 13, 21) have indicated that bacteria growing in vivo may become markedly tolerant to various categories of bactericidal antibiotics. Two major criteria generally used to characterize bacterial tolerance to bactericidal antibiotics are an elevated MBC-to-MIC ratio (>16-fold) and/or decreased elimination rates in kinetic studies (26, 42). In agreement with other investigators working with a variety of experimental systems (6, 21), we have previously described (13) the elevated MBC-to-MIC ratios (>100-fold) of representative beta-lactam, quinolone, and glycopeptide compounds for bacteria removed from chronically infected tissue cage fluids. Most of these data were obtained with MSSA I20 and were completed with time-kill studies showing a slow and incomplete elimination of this strain by eightfold the MICs of either oxacillin, fleroxacin and vancomycin, leading to a decrease in viable counts ranging from 2.0 to 2.5 $\log_{10}$ CFU/ml at 24 h. In the previous study (13), a limited number of time-kill studies were also performed with tissue cage bacteria of MRSA MRGR3, whose viable counts decreased by 2.3 and 2.5 $\log_{10}$ CFU/ml at 24 h by eightfold the MICs of vancomycin and fleroxacin, respectively. Since the elevated MBC-to-MIC ratio of teicoplanin found in the present study for MRSA in tissue cage fluid is not significantly different from those recorded with vancomycin and fleroxacin (13), this parameter does not provide an explanation for the different efficacies of teicoplanin and vancomycin in the treatment of chronic tissue cage infections caused by MRSA. It is possible, however, that the rate of elimination by 16-fold the MIC of teicoplanin of MRSA removed from tissue cage fluid, which is the lowest ever recorded for any antimicrobial agent that is active against strain MRGR3, might be better than the increased MBC-to-MIC ratio in explaining the resistance of tissue cage bacteria to teicoplanin killing in vivo. We can even speculate that the resistance of tissue cage bacteria to teicoplanin killing might even be higher in the in vivo environment than in the ex vivo situation. Previous observations have indeed demonstrated that the phenotypic tolerance expressed by tissue cage bacteria is unstable and is entirely reversible after growth for 4 h in antibiotic-free growth medium (13).

The contribution of the resistant subpopulations that emerged during therapy was also carefully studied in our

model of chronic foreign body infections, since recent reports have stressed the importance of this process (27) during clinical (28, 35) or experimental (28, 29) teicoplanin therapy of *S. aureus* infections. Although initial observations made at the end of teicoplanin monotherapy suggested that the emergence of antibiotic resistance was the reason for an increased proportion of colonies growing on teicoplanin-enriched agar in comparison with the number of organisms grown in vitro, further studies failed to confirm the selection of a teicoplanin-resistant subpopulation by the high-dose regimen. To summarize these findings, we can say that the susceptibility to teicoplanin of tissue cage bacteria differs from that of organisms grown in vitro by three unusual characteristics: (i) the emergence of a "resistant" subpopulation presumably triggered by in vivo conditions, but independently from antibiotic preexposure; (ii) the nonenrichment of the "resistant" subpopulation, despite the presence of continuously high levels of teicoplanin for several days; and (iii) the rapid disappearance of the teicoplanin-"resistant" subpopulation after a single transfer in vitro in antibiotic-free medium. These characteristics do not fit the standard criteria for the emergence of antibiotic resistance. Although we mentioned in a previous report (44) that for isolated colonies of bacteria recovered from tissue cages on agar containing 10 μg of teicoplanin per ml the elevated MICs were maintained during repeated subcultures, this was achieved only by transferring these colonies on teicoplanin-enriched agar.

Although a number of reports of clinical (18, 49) and experimental (3, 40) studies suggest an improved efficacy of a combined therapy (vancomycin plus rifampin) over single-agent regimens against *S. aureus* infections, the superiority of teicoplanin plus rifampin over teicoplanin alone against chronic tissue cage infections caused by MRSA and MSSA was even more impressive because of the ineffectiveness of the glycopeptide alone. The finding of higher levels of teicoplanin in tissue cages during combined therapy with rifampin remains unexplained and has not been reported previously. It is unlikely that such an increase in teicoplanin levels in tissue cage fluid played a major role in the improved efficacy of the combined therapy over that of teicoplanin monotherapy, since the levels of teicoplanin alone were far above the MBC for MRSA. We have previously shown, using the same model, that rifampin is effective as a single agent against chronic tissue cage infections caused by MRSA but that monotherapy with rifampin is eventually compromised by the emergence of drug resistance, which occurred in >75% of the tissue cages (34). Data from the present study suggest that teicoplanin, as was shown previously for vancomycin (34), may help prevent the emergence of rifampin-resistant organisms during therapy of chronic tissue cage infections. Similar data have been found by other investigators (3, 40).

In conclusion, a high-dose regimen of teicoplanin was as effective as vancomycin in preventing experimental foreign body infections in subcutaneously implanted tissue cages, but showed no significant activity against chronic implant-related infections by either a methicillin-resistant or -susceptible strain of *S. aureus*. The levels of teicoplanin in tissue cage fluid were continuously 8- to 16-fold higher than the MBCs for MRSA and could overcome protein binding by tissue cage fluid components. The rapid elimination of bacteria grown in vitro by teicoplanin contrasted with the lack of killing by the same agent of bacteria recovered from infected sites. Since no teicoplanin-resistant subpopulations were selected by the high-dose regimen of teicoplanin, these data suggest that in vivo tolerance to teicoplanin may occur in situations of chronic *S. aureus* infections and may contribute to therapeutic failure. The addition of rifampin to the high-dose teicoplanin regimen led to significant therapeutic activity. Detailed metabolic studies of bacteria growing in vivo, such as the *S. aureus* bacteria found in chronic implant-related infections, need to be performed to elucidate the mechanisms of antibiotic tolerance that are occurring in such bacterial populations.

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