

Successful Single-Dose Teicoplanin Prophylaxis against Experimental Streptococcal, Enterococcal, and Staphylococcal Aortic Valve Endocarditis

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Teicoplanin is a glycopeptide antibiotic that is administered both intramuscularly and intravenously. It has a prolonged half-life and a less toxic profile in comparison to those of vancomycin. The efficacy of a single dose of teicoplanin (18 mg/kg of body weight given intramuscularly) for the prevention of endocarditis due to *Streptococcus oralis*, *Enterococcus faecium*, and methicillin-resistant *Staphylococcus aureus* (MRSA) was evaluated after applying the rabbit model. Vancomycin at a single dose of 30 mg/kg given intravenously was used as the comparative agent for the prevention of endocarditis due to MRSA and *E. faecium*, while ampicillin at a single dose of 40 mg/kg given intravenously was used as the comparative agent for the prevention of endocarditis due to *S. oralis*. Rabbits in the teicoplanin group were infected at 1 h postdosing with $\approx 10^7$ CFU of each strain. Rabbits in the other groups were infected at 0.5 h postdosing with $\approx 10^7$ CFU of *S. oralis* (ampicillin group) or *E. faecium* and MRSA (vancomycin group). All rabbits were sacrificed 5 days later. Teicoplanin and vancomycin protected the animals challenged with *E. faecium* by 87.5 and 50%, respectively, and protected the animals challenged with MRSA by 100 and 92%, respectively. Teicoplanin and ampicillin protected the animals challenged with *S. oralis* by 100 and 77%, respectively. Prevention of endocarditis by teicoplanin was likely to be due to a prolonged inhibition of bacterial growth by the sustained supra-MICs. It is concluded that teicoplanin is very effective in preventing experimental streptococcal, enterococcal, and staphylococcal endocarditis and may be an attractive alternative antibiotic in patients allergic to β -lactams, especially in the outpatient setting.

Infective endocarditis (IE), although relatively uncommon, is a severe disease with high morbidity and mortality rates. Almost any type of structural heart disease may predispose an individual to IE, especially when the defect results in a turbulence of blood flow. Gram-positive cocci are the most frequent etiologic agents, being responsible for up to 80 to 90% of the cases of IE (26, 29). Despite uncertainties concerning the effectiveness of prophylactic measures (12, 15), prophylaxis with antibiotics active against these microorganisms is indicated in the majority of patients with an underlying valve disorder who are going to undergo any procedure that could result in transient bacteremia (8, 9). Amoxicillin is the primary prophylactic regimen for most patients (8). However, it is known that approximately 11% of the streptococci that cause IE are tolerant to penicillin (9, 33), an *in vitro* phenomenon that has been shown to influence the efficacies of β -lactam antibiotics in the prophylaxis of streptococcal (16, 25) and staphylococcal (36) IE. On the other hand, the rates of resistance of enterococci to β -lactams and aminoglycosides have been increasing in recent years (10, 20). In patients allergic to β -lactam antibiotics, vancomycin is the recommended antibiotic for prophylaxis, especially in high-risk patients (e.g., patients with previous endo-

carditis or prosthetic valve) who undergo genitourinary or gastrointestinal procedures (8, 9, 18, 38). The need for slow intravenous infusion and the severe adverse reactions like collapse and the "red man" syndrome, especially during the administration of the first dose, are some of the disadvantages of vancomycin (19, 24). Thus, the search for alternative prophylactic agents is warranted.

Teicoplanin is a glycopeptide antibiotic with a spectrum of activity and a mechanism of action similar to those of vancomycin (5, 32). Unlike vancomycin, however, teicoplanin has a prolonged half-life (>100 h) and a remarkable postantibiotic effect (5), thus allowing for once-daily administration, while it is well tolerated when given intramuscularly (4, 5, 37). Therefore, it represents an attractive alternative to vancomycin, especially in the outpatient setting.

Because of the lack of controlled studies regarding the prophylactic efficacies of antibiotics in humans, the guidelines for prophylaxis for IE are based on clinical experience and on *in vitro* and animal studies. This study was designed in order to evaluate the prophylactic efficacy of teicoplanin against the most common etiologic agents responsible for the development of IE, namely, viridans group streptococci and *Staphylococcus aureus*, and against *Enterococcus faecium* by applying the rabbit model.

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MATERIALS AND METHODS

Microorganisms. The three strains used in this study were isolated from cultures of blood from patients with endocarditis and were identified by standard methods. The strain of *S. aureus* has also been used in a previous study of ours (22). The species of the strain of the viridans group streptococcus was determined to be *Streptococcus oralis*. The bacteria were stored at -80°C in skim milk and were subcultured on blood agar plates 3 days before each experiment.

Susceptibility testing. The MICs of teicoplanin, vancomycin, oxacillin (plus 2% NaCl), ampicillin, and penicillin were determined by a microdilution technique in volumes of 0.1 ml by using logarithmic-growth-phase inocula of *E. faecium* and *S. aureus* in cation-supplemented Mueller-Hinton II broth and *S. oralis* in Todd-Hewitt broth (BBL Microbiology Systems, Cockeysville, Md.) adjusted to a final inoculum of $\approx 5 \times 10^5$ per ml. The concentration range of teicoplanin (supplied by Marion Merrell Dow, Milan, Italy) tested was from 0.015 to 512 $\mu\text{g/ml}$, while the concentration range of all other antibiotics (supplied by the commercial route) was from 0.125 to 512 $\mu\text{g/ml}$. The MIC was defined as the lowest concentration causing no visible turbidity after incubation for 18 h at 35°C (*E. faecium* and *S. aureus*) and 37°C (*S. oralis*). The minimum bactericidal concentration (MBC) was defined as the lowest concentration of antibiotic that yielded a $\geq 99.9\%$ reduction of the initial inoculum after subculturing 0.1 ml from each clear well onto blood agar plates (BAPs; Becton Dickinson, Cockeysville, Md.) and incubating the plates for 48 h at 37°C (*S. oralis*) and for 24 h at 35°C (*S. aureus* and *E. faecium*). Tolerance was defined as an MIC/MBC ratio of 1/32 or greater. The production of β -lactamase by the *E. faecium* strain was tested by using nitrocefin disks.

Time-kill curves. Killing kinetics were determined for all three strains. Overnight cultures in Mueller-Hinton broth (Todd-Hewitt broth for *S. oralis*) were used to prepare inocula of $\approx 5 \times 10^6$ CFU per ml. These were added both to the antibiotic-containing tubes and to the appropriate control tubes. The final antibiotic concentrations tested in all experiments were 20 μg of teicoplanin per ml, 40 μg of vancomycin per ml, and 25 μg of ampicillin per ml. A teicoplanin concentration of 1 $\mu\text{g/ml}$ was also tested against the methicillin-resistant *S. aureus* (MRSA) strain. The concentration of 20 μg of teicoplanin per ml was chosen because it represents the mean concentration of teicoplanin in rabbit serum 1 h after the intramuscular administration of a single dose of 18 mg/kg of body weight. At time zero and at 5 and 24 h of incubation, the number of growing colonies was determined quantitatively. To eliminate the carryover effect, specimens from all tubes were plated onto appropriate agar plates after six appropriate dilutions, with a 1-log inoculum difference between each dilution (10^{-1} to 10^{-6}), and the plates were incubated for 24 to 48 h.

Induction and prophylaxis of endocarditis. Nonbacterial thrombotic endocarditis of the aortic valve was induced in female White rabbits weighing 2.0 to 3.0 kg by using the model described by Perlman and Freedman (23), with the polyethylene catheter left in place throughout the experiment. Twenty-four hours after catheterization, the rabbits were randomly assigned to a control group, a group receiving teicoplanin at a single dose of 18 mg per kg of body weight intramuscularly, a group receiving vancomycin at a single dose of 40 mg per kg of body weight intravenously, and a group receiving ampicillin at a single dose of 40 mg per kg of body weight intravenously. Ampicillin was given as prophylaxis only against *S. oralis*, while vancomycin was given as prophylaxis against *S. aureus* and *E. faecium*. Teicoplanin was given as prophylaxis against all three strains. The dose of teicoplanin was chosen because in pilot studies it was found to achieve peak levels in rabbit serum similar to those obtained in human serum 45 min after the administration of a single intravenous dose of 3 mg/kg of body weight (34) and trough (at 24 h) levels close to 10 $\mu\text{g/ml}$, which is the recommended trough level for optimal treatment in humans (27). This dose also has been used successfully by Chambers and Kennedy (6) for the treatment of experimental endocarditis in rabbits. The doses of vancomycin and ampicillin were chosen because they have been used in previous studies of endocarditis prophylaxis (2, 13, 21). Animals treated with teicoplanin and animals treated with ampicillin or vancomycin were challenged 1 and 0.5 h later, respectively, with an inoculum of $\approx 10^7$ CFU of *S. oralis*, *E. faecium*, or *S. aureus*. This inoculum was suspended in 1 ml of saline and was injected via the marginal ear vein. The rabbits were sacrificed 5 days (120 h) after bacterial challenge by rapid intravenous injection of 30 mg of sodium phenobarbital per kg in order to avoid the carryover effect, since from pilot studies by our group no detectable levels of teicoplanin were observed 96 h after the administration of teicoplanin. Use of this time interval could also allow for the detection of any possible relapses due to the regrowth of persistent, viable bacteria (in small numbers) in vegetations after the complete elimination of antibiotics from the body. At the time of sacrifice, aortic valve vegetations were excised, weighed, homogenized in 2 ml of saline, and quantitatively cultured, in duplicate, onto BAPs (*S. oralis*), BAPs and Staphylococcus agar-110 plates (*S. aureus*), and BAPs and MacConkey agar plates (*E. faecium*) after eight dilutions, with a 1-log inoculum difference between each dilution. The colonies were counted after incubation for 24 h at 35°C or 48 h at 37°C for *S. aureus* and *E. faecium* or *S. oralis*, respectively. The results were expressed as the \log_{10} numbers of CFU per gram of vegetation. The lower limit of detection by this method was 2 \log_{10} CFU per gram of vegetation. The macroscopic and/or bacteriologic data obtained at the time of sacrifice provided

TABLE 1. MICs and MBCs of teicoplanin and several other antimicrobial agents for *S. oralis*, *E. faecium*, and *S. aureus*

Antibiotic	MIC/MBC ($\mu\text{g/ml}$) for the following:		
	<i>S. oralis</i>	<i>E. faecium</i>	<i>S. aureus</i>
Penicillin	0.12/1	>4/>4	ND ^a
Ampicillin	<0.12/0.5	16/>500	ND
Oxacillin	ND	ND	64/128
Vancomycin	1/32	1/32	1/1
Teicoplanin	<0.015/32	0.25/>256	1/1

^a ND, not determined.

confirmation of the successful induction of vegetative endocarditis. Rabbits with sterile vegetations were considered uninfected.

Antibiotic concentrations in serum. Teicoplanin levels were determined in serum samples obtained at 1, 24, 48, 72, 96, and 120 h postdosing. An agar well bioassay technique was applied (1). *Bacillus subtilis* ATCC 6633 was used as the test organism, and normal rabbit serum was used as the diluent. The lower limit of detection of this assay was 0.4 $\mu\text{g/ml}$. Ampicillin and vancomycin levels were determined in serum samples obtained at 30 min, 1 h, and 2 h postdosing. For ampicillin, an agar well bioassay technique with *Micrococcus luteus* as the test organism was applied. Serum vancomycin levels were determined by the fluorescence polarization immunoassay (TDx system; Abbott Laboratories, Abbott Park, Ill.).

Statistical analysis. To compare the differences between sterile (successful prophylaxis) and nonsterile vegetations, the Fisher exact test for probabilities was used. A *P* value of ≤ 0.05 was considered significant.

RESULTS

MICs and MBCs. The MICs and MBCs of teicoplanin, vancomycin, penicillin, ampicillin, and oxacillin for the three strains tested are presented in Table 1. For the *E. faecium* strain the MBCs of penicillin, ampicillin, vancomycin, and teicoplanin were high, which is a common phenomenon for these strains when cell wall-active antibiotics are tested. This strain was not a β -lactamase producer. The *S. oralis* strain was tolerant of teicoplanin and vancomycin but not penicillin. The *S. aureus* strain was methicillin resistant (MRSA).

Killing curves. The in vitro killing activities of the three antibiotics studied are presented in Fig. 1, 2, and 3. Teicoplanin and vancomycin exhibited bacteriostatic effects against both *S. oralis* (Fig. 1) and *E. faecium* (Fig. 2). Against *S. aureus* (Fig. 3), both antibiotics exhibited a bactericidal effect at 24 h. Even the low concentration of 1 mg of teicoplanin per liter was bactericidal against MRSA (Fig. 3). Ampicillin was bactericidal against *S. oralis* (Fig. 1).

Antibiotic pharmacokinetics in serum. The pharmacokinetics of teicoplanin in serum are presented in Fig. 4. The mean \pm standard deviation (SD) concentrations of teicoplanin in serum 1, 24, 48, and 72 h after the administration of a single intramuscular dose of 18 mg/kg were 19.2 ± 7.3 $\mu\text{g/ml}$ ($n = 13$), 9.8 ± 4.2 $\mu\text{g/ml}$ ($n = 14$), 3.5 ± 2.6 $\mu\text{g/ml}$ ($n = 8$), and 1.5 ± 0.6 $\mu\text{g/ml}$ ($n = 6$), respectively. At 96 and 120 h postdosing none of the rabbits tested ($n = 5$ for each time point) had detectable teicoplanin levels. The mean \pm SD concentrations of vancomycin in serum 30 min, 1 h, and 2 h after the administration of a single intravenous dose of 40 mg/kg were 71.5 ± 13.7 $\mu\text{g/ml}$ ($n = 5$), 51.1 ± 7.1 $\mu\text{g/ml}$ ($n = 4$), and 37.6 ± 9.9 $\mu\text{g/ml}$ ($n = 4$), respectively. The mean \pm SD concentrations of ampicillin in serum 30 min, 1 h, and 2 h after the administration of a single intravenous dose of 40 mg/kg were 13.5 ± 6.8 $\mu\text{g/ml}$ ($n = 5$), 7.3 ± 3.2 $\mu\text{g/ml}$ ($n = 5$), and 1.2 ± 0.5 $\mu\text{g/ml}$ ($n = 5$), respectively.

Prophylaxis against endocarditis. The results of prophylaxis against the three strains tested are presented in Table 2. Ninety-two, 85, and 88% of the control animals challenged with 10^7

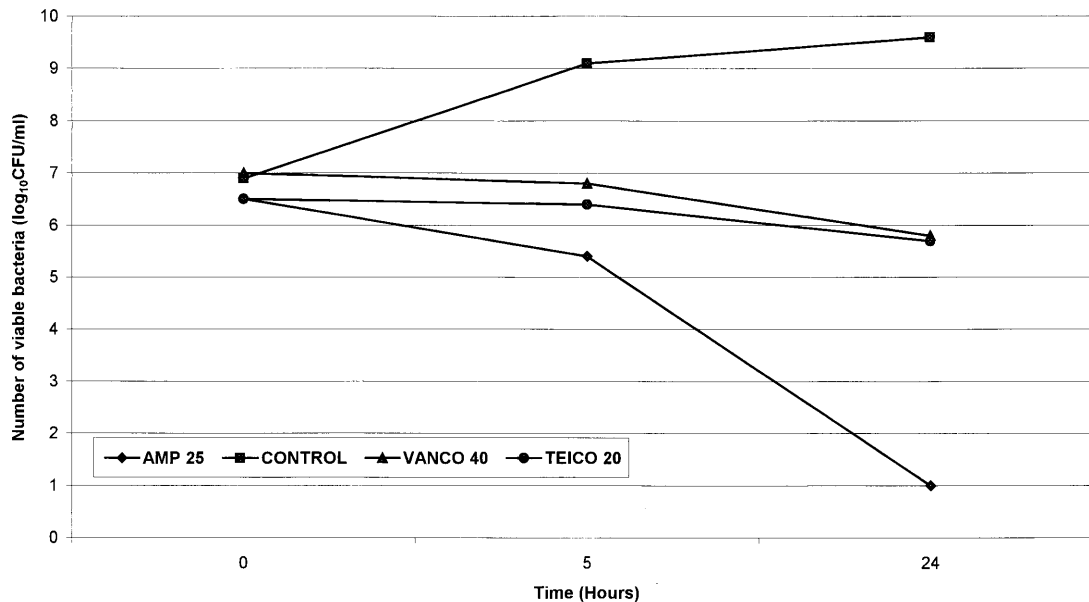


FIG. 1. Time-kill curves for *S. oralis* by teicoplanin at 20 mg/liter (TEICO 20), vancomycin at 40 mg/liter (VANCO 40), and ampicillin at 25 mg/liter (AMP 25) at an inoculum of 10^6 to 10^7 CFU/ml. Data are the means of two separate experimental runs.

CFU of *S. oralis*, *E. faecium*, and *S. aureus*, respectively, developed infected vegetations. In rabbits challenged with this very high inoculum, teicoplanin completely prevented endocarditis due to *S. aureus* and *S. oralis* ($P < 0.001$) but failed to prevent endocarditis in 2 of 16 (12.5%) animals challenged with the *E. faecium* strain. Despite that, the difference in the sterility rate from that for the control animals was still statistically significant ($P < 0.001$). The numbers of CFU per gram of vegetation in the two animals challenged with *E. faecium* that failed to respond to the administration of teicoplanin were similar to those in the control animals (9.8 and 8.0 CFU/g, respectively, versus 8.6 CFU/g [mean values]). Vancomycin

prevented endocarditis in all but one animal challenged with MRSA, but it failed to prevent endocarditis in 50% of the animals challenged with *E. faecium* ($P = 0.044$ versus teicoplanin; $P = 0.097$ versus controls). Finally, ampicillin prevented endocarditis due to *S. oralis* in 77% of the challenged animals ($P = 0.064$ versus controls).

DISCUSSION

This study has evaluated the efficacy of a single dose of teicoplanin for the prophylaxis of experimental endocarditis due to *S. oralis*, *E. faecium*, and *S. aureus* in rabbits. Teicopla-

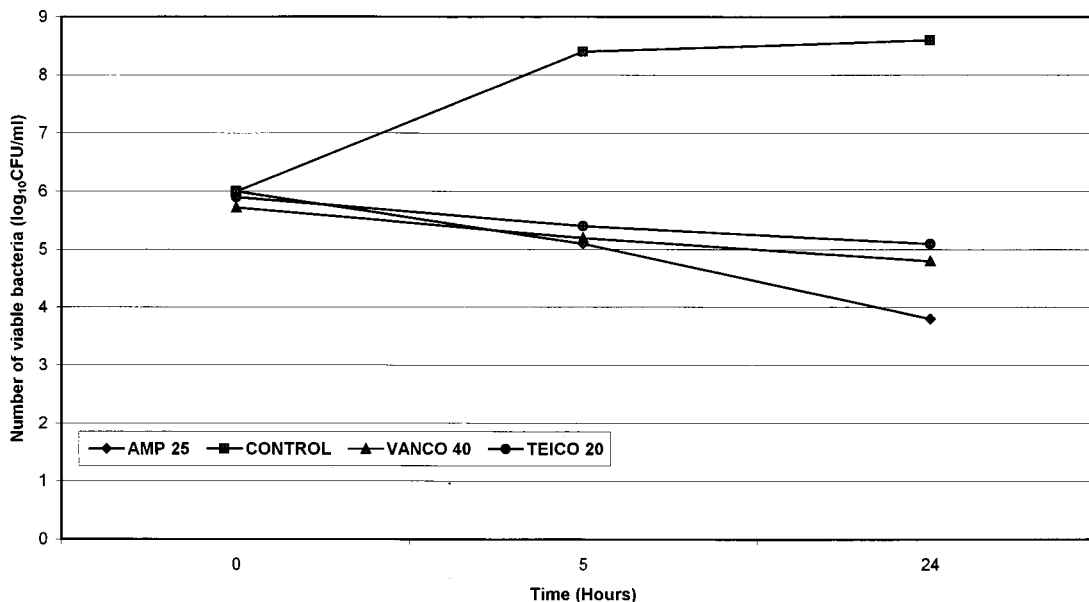


FIG. 2. Time-kill curves for *E. faecium* by teicoplanin at 20 mg/liter (TEICO 20), vancomycin at 40 mg/liter (VANCO 40), and ampicillin at 25 mg/liter (AMP 25) at an inoculum of 10^6 CFU/ml. Data are the means of two separate experimental runs.

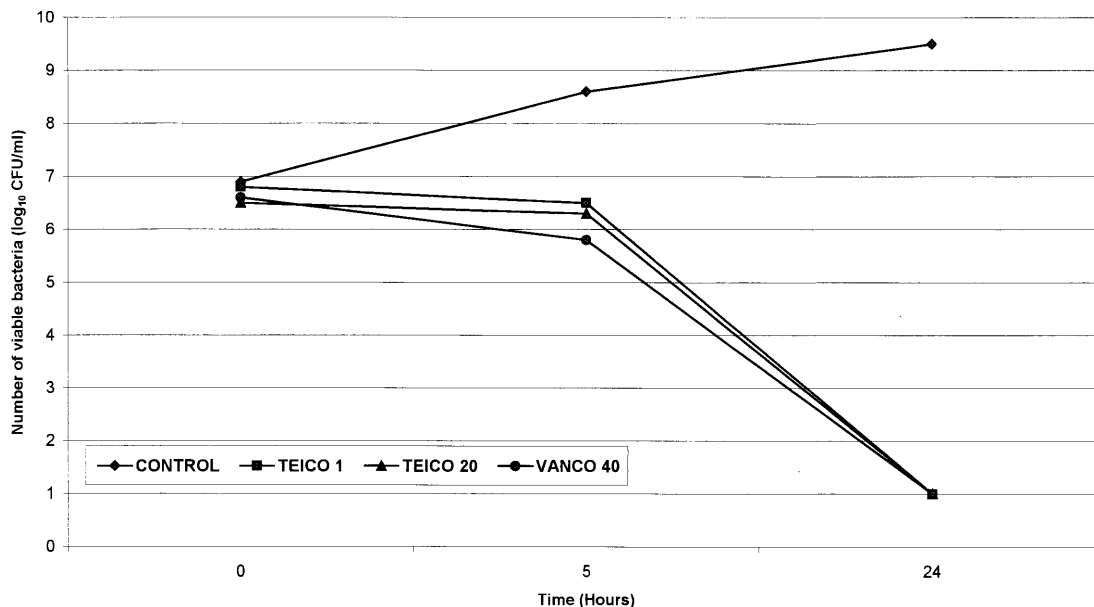


FIG. 3. Time-kill curves for *S. aureus* (MRSA) by teicoplanin at 1 and 20 mg/liter (TEICO 1 and TEICO 20, respectively) and vancomycin at 40 mg/liter (VANCO 40) at an inoculum of 10^6 to 10^7 CFU/ml. Data are the means of two separate experimental runs.

nin was completely successful against a very high inoculum of *S. oralis* or *S. aureus*, while it partially prevented endocarditis due to *E. faecium*. This protection was conferred in the absence of in vitro killing of *S. oralis* and *E. faecium*. On the contrary, vancomycin prevented endocarditis in only 50% of the animals challenged with *E. faecium*. Against *S. aureus*, both, teicoplanin and vancomycin were bactericidal in vitro and were very protective in vivo. Since inoculum amounts as large as the inoculum that we used (10^7 CFU) are unlikely to be released during dental procedures on humans (15), these

experiments provide a most stringent test for antibiotic efficacy.

Studies done by Bernard et al. (3), Glauser et al. (13), Moreillon et al. (21), Malinverni et al. (17), and Scheld et al. (30) more than a decade ago have characterized three possible mechanisms that are involved in the prophylactic efficacies of antibiotics against endocarditis: (i) initial intravascular killing of challenge inocula at supra-MBC antibiotic levels in serum, (ii) antiadherence effect, and (iii) prolonged growth inhibition of vegetation surface-adhered organisms. Moreillon et al. (21)

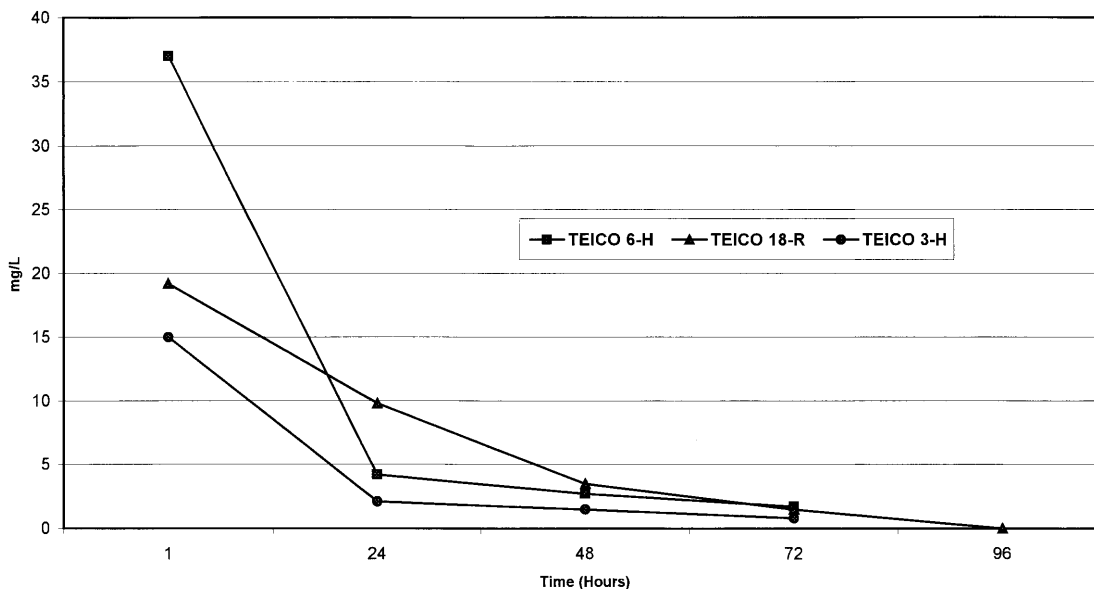


FIG. 4. Concentrations of teicoplanin in rabbit sera after the administration of a single dose of 18 mg per kg of body weight intramuscularly (TEICO 18-R; data are the mean of the concentrations in at least five animals at each time point) and in human serum after the administration of a single intravenous dose of 3 mg/kg (TEICO 3-H) or 6 mg/kg (TEICO 6-H) (data adapted from a previous report [34]).

TABLE 2. Results of prophylaxis with teicoplanin, vancomycin, or ampicillin in rabbits challenged with *S. oralis*, *E. faecium*, or *S. aureus*

Regimen	No. of infected animals/total no. (%)			Mean log CFU/g of vegetation		
	<i>S. oralis</i>	<i>E. faecium</i>	<i>S. aureus</i>	<i>S. oralis</i>	<i>E. faecium</i>	<i>S. aureus</i>
Controls	11/12 (92) ^{a,b}	11/13 (85) ^{a,c}	14/16 (88) ^a	8.0 ± 1.0	8.2 ± 1.3	9.2 ± 1.4
Teicoplanin	0/18 (0) ^a	2/16 (12.5) ^{a,d}	0/16 (0) ^a		9.8, 8.0	
Vancomycin	ND ^e	6/12 (50) ^{c,d}	1/12 (8) ^a	ND	8.2 ± 0.5	7.7
Ampicillin	3/13 (23) ^b	ND	ND	8.1 ± 1.9	ND	ND

^a $P < 0.001$ (Fisher exact test).

^b $P < 0.064$ (Fisher exact test).

^c $P = 0.097$ (Fisher exact test).

^d $P = 0.044$ (Fisher exact test).

^e ND, not determined.

suggested that in the absence of bacterial killing, growth inhibition rather than inhibition of bacterial adherence may be the possible mechanism of successful antibiotic prophylaxis of endocarditis, allowing the bacteria to be cleared from the damaged valves. When large inocula were used, prolonged inhibitory concentrations might circumvent the limited efficacies of antibiotics in preventing endocarditis. Indeed, Glauser and Francioli (14), in a summary of their experimental observations of antibiotic prophylaxis of streptococcal endocarditis, concluded that single doses of antibiotics such as amoxicillin, penicillin G, clindamycin, and vancomycin are successful in reliably preventing endocarditis induced by bacterial inocula corresponding to the 90% infective dose, while multiple doses are needed in order to achieve prolonged inhibitory concentrations when bacterial challenges higher than the 90% infective dose are used. In another study, by Bayer and Tu (2), the prophylactic efficacy of vancomycin against experimental *E. faecalis* endocarditis seemed to be related to the prolonged inhibitory activities in serum induced by vancomycin. In the study by Entenza et al. (11), teicoplanin (single intravenous dose of 7 mg/kg) was superior to vancomycin (single intravenous dose of 15 mg/kg) for the prevention of *E. faecalis* endocarditis in rats. In the latter study, a single intravenous dose of teicoplanin produced levels in serum which were above the MICs for more than 12 h after the injection, which is in contrast to the levels of vancomycin in serum, which were above the MICs for only 4 h. The investigators suggested that it is likely that the better prophylactic effect of teicoplanin was due to a more sustained inhibition of bacterial growth by teicoplanin. The results of the studies mentioned above are in accordance with the results of the present study, in which the prolonged growth inhibition achieved by the sustained supra-MIC levels of teicoplanin, even 3 days after the intramuscular administration of the drug, seem to be the most plausible explanation for the prophylactic efficacy of teicoplanin against the tolerant strains of *E. faecium* and *S. oralis* that were used. However, the possible prolonged antiadherence effect of teicoplanin was not evaluated in our study. On the other hand, it is very likely that the excellent prophylactic effect of teicoplanin against *S. aureus* was due to both the rapid intravascular killing, as suggested by the time-kill curves, and the prolonged inhibition of the bacterial growth on vegetations.

The intramuscular administration of teicoplanin has been proved to give better therapeutic results than the intravenous administration in the study of experimental endocarditis due to *S. aureus* in rabbits by Chambers and Kennedy (6). A possible explanation given by those investigators is that higher trough levels, longer periods of time above a critical concentration, and perhaps, more time for penetration into the vegetation were obtained with the intramuscular regimen. Furthermore, the fact that teicoplanin is retained at the periphery of the

vegetations and fails to diffuse into their core (7) may contribute to the reported failures of teicoplanin for the treatment of staphylococcal endocarditis (37), but as suggested by our results and the results of the study by Entenza et al. (11), this phenomenon does not impair the prophylactic efficacy of teicoplanin, probably because the bacteria in prophylaxis studies are at the surface of the vegetation and are not yet protected by fibrin.

To our knowledge this is the first experimental study of the prophylactic efficacy of teicoplanin against a strain of viridans group streptococcus. Our promising results are in agreement with those of a clinical study of the prophylaxis of streptococcal bacteremia in dental patients, in which teicoplanin, given as a single intravenous bolus injection of 400 mg after the induction of anesthesia, was clearly effective in reducing the prevalence of detectable postextraction bacteremia, because a viridans group streptococcus was isolated from the blood of only 1 of 40 patients, whereas viridans group streptococci were isolated from the blood of 13 of 40 patients in the control group and 10 of 40 patients in the amoxicillin group (31).

Two studies of the prophylactic efficacy of the teicoplanin against experimental *S. aureus* infections were published recently. Voorn et al. (35) reported that teicoplanin had very good prophylactic efficacy against a tolerant strain of *S. aureus* and its nontolerant variant when doses of 6 and 30 mg/kg were administered. The results were poor when the lower dose was given to the animals challenged with the tolerant strain. However, this very low dose of teicoplanin was still efficacious against the nontolerant strain. Finally, Schaad et al. (28) reported that a high dose (30 mg/kg) of teicoplanin was as effective as vancomycin in preventing experimental foreign body infections due to *S. aureus* in subcutaneously implanted tissue cages. The results of these studies are also in accordance with the results of the present study.

In conclusion, in the present experimental study, teicoplanin was proved to be very efficacious for the prophylaxis of endocarditis caused by a tolerant strain of *S. oralis* and an MRSA strain. Its prophylactic efficacy was comparable to that of established antibiotic regimens, namely, vancomycin for MRSA and ampicillin for viridans group streptococci. Teicoplanin was partially successful against a tolerant, non- β -lactamase-producing strain of *E. faecium*. Nevertheless, its prophylactic efficacy against *E. faecium* was still significant and superior to that of vancomycin. These results and the results of the previously mentioned clinical and experimental studies (11, 31, 35) suggest that teicoplanin given as a single dose of 400 mg intramuscularly or intravenously should be considered an alternative to vancomycin for the prophylaxis of endocarditis, especially in the outpatient setting.

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