ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1989, p. 1329–1334
0066-4804/89/081329-06$02.00/0

Vol. 33, No. 8

Teicoplanin in the Treatment of Gram-Positive-Bacterial Endocarditis

P. MARTINO,[1]* M. VENDITTI,[2] A. MICOZZI,[1] C. BRANDIMARTE,[2] G. GENTILE,[1] C. SANTINI,[2] AND P. SERRA[2]

Cattedra di Ematologia, Dipartimento di Biopatologia Umana,[1] and Patologia Medica III,[2] Università "La Sapienza," 00161 Rome, Italy

Received 28 November 1988/Accepted 18 May 1989

Intravenous teicoplanin has been used to treat 23 cases of gram-positive-bacterial endocarditis, usually with 3 to 7 mg/kg every 12 h on the first day, followed by 3 to 7 mg/kg every 24 h. For some cases (staphylococcal and enterococcal endocarditis), the dosage was 8 to 14.4 mg/kg per day and/or other antibiotics were given. The mean duration was 48.2 days (range, 23 to 130 days). Of 23 patients, 21 (91.3%) had negative cultures or were cured. A total of 18 patients were treated with teicoplanin alone; of these, 4 had surgery, and all (except 2 who relapsed) were cured. Teicoplanin was combined with one or more antibiotics in five cases; in all cases appropriate cultures were negative, but three patients died during therapy or follow-up. Mild renal impairment was seen in two patients; both were receiving teicoplanin in combination with an aminoglycoside. We conclude that intravenous teicoplanin administered once a day at doses of 7 to 14 mg/kg per day is well tolerated, easy to administer, and may represent an efficacious therapy for gram-positive-bacterial endocarditis.

Gram-positive microorganisms still are the most frequent cause of infective endocarditis (6, 24). Moreover, new species which are resistant to several antibiotics (i.e., JK corynebacteria) are emerging (10, 16, 19). Teicoplanin is a glycopeptide antibiotic with an antibacterial spectrum similar to that of vancomycin which is active against multiple-antibiotic-resistant, gram-positive bacteria (4, 9, 13, 22). However, it has a longer elimination half-life, which allows once-a-day administration, and appears to be well tolerated (8, 14, 23). Although studies with animal models suggested good results with teicoplanin, alone or in combination with other antibiotics, for the treatment of infective endocarditis and other life-threatening infections (3, 5, 20), the results of recent clinical trials are somewhat conflicting (1, 8, 11, 14, 25). Moreover, only a few gram-positive-bacterial endocarditis cases were included in the above studies. The majority of these cases were caused by *Staphylococcus* species and were treated with a standard dose of 400 mg on the first day followed by 200 mg/day afterwards. Such a schedule of teicoplanin administration proved to be inadequate for the therapy of severe staphylococcal infections in a recent clinical trial (1). We report here our 3 years of experience with 23 cases of gram-positive-bacterial endocarditis, most of which were treated with doses of teicoplanin higher than those previously used.

MATERIALS AND METHODS

Patients. All subjects were inpatients in various divisions of the Policlinico Umberto I, University of Rome. They were initially considered eligible for the study if they had clinical syndromes consistent with gram-positive-bacterial endocarditis. Only those cases fitting recently recommended strict case definitions were included in the analysis of the results (15, 24). For almost all patients two-dimensional echocardiography was performed, and specific attention was paid not only to the valvular structures but also to the right chambers in those who had had chronic indwelling intracardiac catheters. The diagnosis of vegetation was made according to published criteria (7). To diagnose catheter-related right-side infective endocarditis the following diagnostic criteria, modified from Robbins et al. (15), were adopted. Echocardiographically demonstrable vegetations of either the tricuspid and pulmonic valves or of the right atrium endocardium and pyrexia persisting or recurring even after catheter removal were major criteria, and multiple, temporally spaced, positive blood cultures even after catheter removal; evidence of septic pulmonary emboli; murmur compatible with tricuspid or pulmonic valve involvement; and absence of systemic emboli were minor criteria. Either two major criteria or one major and three of the four minor criteria had to be satisfied to diagnose catheter-related right-side infective endocarditis.

Nineteen patients received antibiotics before this study. For 15 of these, persistent bacteremia (according to the criteria of Von Reyn et al.) (24) was documented before initiating intravenous teicoplanin. In one additional patient with *Staphylococcus aureus* right-side infective endocarditis, intermittent bacteremia was found before trial therapy. The remaining three patients were febrile but not bacteremic after discontinuation of previously administered antibiotics. One of these was a patient with a leakage of the aortic prosthesis caused by an *S. aureus* infection documented at surgery 24 h before teicoplanin therapy was started. The second patient had a chronic myeloid leukemia in blastic crisis and was persistently febrile under a previous treatment course with ceftriaxone, amikacin, and co-trimoxazole. Teicoplanin was administered because a catheter-related JK corynebacterium right-side endocarditis was diagnosed. The third patient had a culture-negative infection of the mitral valve documented at surgery. A previous treatment with oral ampicillin and dicloxacillin had been discontinued 7 days before valve replacement and the start of teicoplanin therapy in this patient.

We excluded from the study patients with moderate renal impairment (serum creatinine higher than 3 mg/100 ml), patients with pathogens resistant to teicoplanin, pregnant or lactating women, and moribund patients.

Infection documentation. On the basis of this protocol, 26 patients with presumed gram-positive-bacterial endocarditis were initially included in the study. Of these, two patients

* Corresponding author.

with *S. aureus* endocarditis were excluded from the analysis of the results because they died within 12 h after therapy was begun. Another patient, initially diagnosed with catheter-related right-side infective endocarditis and successfully treated with a 28-day teicoplanin course, was also excluded because he failed to meet the above-mentioned case definition criteria. Of the remaining 23 patients, 6 (26.1%) were categorized as having definite endocarditis confirmed by histology and culture from surgery or autopsy (24). Two patients (8.7%) were categorized as having probable endocarditis because of the concomitant presence of persistent bacteremia and predisposing heart disease with vascular phenomena in one case (Osler nodes) and with a new regurgitant murmur in the other one (24). Seven patients (30.4%) were categorized as having possible endocarditis on the basis of persistent bacteremia and predisposing heart disease (24). Seven patients (30.4%) were diagnosed as having right-side infective endocarditis clinically according to the criteria of Robbins et al. (15). Of 23 infective endocarditis cases, 20 were evaluated by two-dimensional echocardiography, and endocardial vegetations were documented in 19 patients.

One additional patient diagnosed as having right-side infective endocarditis for whom echocardiographic examination was not performed was included. This was a 72-year-old woman who underwent removal of the generator of her transvenous pacemaker for an *S. aureus* infection. Since the patient refused surgery, the transvenous electrodes were left in place and a new transvenous pacemaker was implanted. She subsequently developed an *S. aureus* bacteremia which relapsed after a 14-day course with cefoxitin and gentamicin. We hypothesized an endocardial infection of the previous pacemaker lead insertion site due to spontaneous leakage of the ventricular lead during teicoplanin therapy. No other identifiable source of *S. aureus* bacteremia was found in this patient.

Microbiologic studies. Aerobic and anaerobic blood cultures were obtained from each patient before initiation of therapy. Pathogens were identified by standard methods and tested for susceptibility to teicoplanin, penicillin, vancomycin, aminoglycosides, and, for staphylococcal isolates, oxacillin and rifampin. Initial evaluation of antibiotic susceptibility was performed by the disk diffusion method, and resistance to teicoplanin was defined as a zone inhibition diameter of less than 14 mm. MICs were measured by a macrodilution procedure either in Mueller-Hinton broth supplemented with 5% lysed horse blood with saponin when viridans group streptococci were assayed or in brain heart infusion broth with 5% lysed horse blood when JK corynebacteria were tested (12, 21). MBCs were also determined (21).

After 5 to 7 days from the trial treatment start and then afterwards once a week, serum teicoplanin levels and the serum bactericidal activity (SBA) titers were measured at 1 h (peak) and 24 h (trough) after intravenous infusion. Serum teicoplanin levels were measured by the agar diffusion method, using *Bacillus subtilis* ATCC 6633 as the test strain; a solid-phase enzyme receptor assay was performed when teicoplanin was used in combination with other antibiotics (2). SBA levels of each patient during the trial were measured by using a macrodilution procedure in Mueller-Hinton broth (17).

Treatment regimen. After patients had given their oral consent to the study, they were given an initial dose of 3 to 7 mg/kg every 12 h on the first day of therapy followed by the same dosage at 24-h intervals. Whenever necessary, the daily dosage was increased in an attempt to achieve adequate SBA levels (26). Teicoplanin was supplied in 200-mg vials by Gruppo Lepetit S.P.A. The drug was dissolved in 100 ml of 5% glucose in water and administered by a 15-min intravenous infusion.

TABLE 1. Teicoplanin in the treatment of 23 cases of gram-positive-bacterial endocarditis

Treatment(s)	No. of cases	No. (%) of:		
		Cures	Relapses	Deaths[a]
Teicoplanin alone	14	12 (85.7)	2 (14.7)	0
Teicoplanin + other antibiotics	4	4 (100)	0	2
Teicoplanin + other antibiotics + surgery	1	1 (100)	0	1
Teicoplanin + surgery	4	4 (100)	0	0
Total		21 (91.3)	2 (8.7)	3 (13)

[a] During therapy or follow-up.

Evaluation of teicoplanin efficacy and safety. Response to trial therapy was assessed on clinical and microbiological grounds. Therefore, a cure was defined as disappearance of symptoms and signs of infection with negative cultures (from blood and/or endocardium taken at the surgery or autopsy) without relapse within 3 months after the end of teicoplanin treatment. Blood cultures were done for all patients 1 month after the end of antibiotic treatment. Laboratory tests for renal, liver, and hemopoietic functions were performed weekly during the treatment and, when necessary, during the follow-up.

RESULTS

Of the 22 patients given teicoplanin for 23 episodes of gram-positive-bacterial endocarditis, 16 were men and 6 were women, with a mean age of 46.9 years. There were 15 left-side infective endocarditis cases and 8 right-side infective endocarditis cases. The majority of cases were natural valve endocarditis (19 cases); 2 were infections of a prosthetic valve and 2 were infections of the right atrium. Mean duration of intravenous teicoplanin treatment was 48.2 days, with a range of 23 to 130 days.

Each patient had at least one of the following underlying conditions: heart valvular disease (13 patients), moderate to severe congestive heart failure (6 patients), central venous catheter (5 patients), bone marrow transplantation (5 patients), drug addiction (2 patients), pacemaker insertion (1 patient), and renal failure (1 patient).

Teicoplanin was used as the sole therapy for 14 cases, whereas a combination with other antibiotics (4 cases), valve replacement (4 cases) or both (1 case) were required for the remaining 9 cases (Table 1). Overall, 21 of 23 cases (91.3%) became bacteria free. A relapse occurred in one patient with endocarditis caused by *Streptococcus bovis* and in one with endocarditis caused by *Enterococcus faecalis*. Death occurred in three cases (13%) during or after therapy.

Viridans group streptococci and *Streptococcus bovis* endocarditis. There were eight episodes of infective endocarditis caused by viridans group streptococci (five cases) or *Streptococcus bovis* (three cases) (Table 2). Cases 4 and 5 were two episodes in the same patient. All streptococcal isolates were highly susceptible to teicoplanin, with MBCs of <0.5 mg/ml. An initial dose of 3 to 6 mg/kg per day always produced peak levels of SBA equal to or higher than 1:64.

TABLE 2. Teicoplanin therapy of viridans group streptococci and *Streptococcus bovis* endocarditis: relationship between in vitro susceptibility of the pathogen, drug and bactericidal levels in serum, and clinical outcome

Case no.	Infection site[a]	Etiology	MIC/MBC (μg/ml)	Dosage (mg/kg/per day) (serum creatinine [mg/100 ml])[b]	Levels in serum (μg/ml) (SBA) at:		Days of therapy	Outcome and clinical notes
					1 h	24 h		
1	MV	*S. salivarius*	0.06/0.06	3.7 (1)	25 (>1:512)	11 (>1:512)	42	Cure; follow-up, >6 mo
2	AV	*S. mutans*	0.06/0.5	6 (1.6)	37 (1:64)	9 (1:8)	49	Cure; follow-up, >6 mo
3	AV	*S. sanguis*	0.12/0.12	4.4 (0.8)	22 (>1:512)	8 (>1:512)	42	Cure; follow-up, >6 mo
4	MV	*S. mitis*	0.03/0.03	3.7 (0.8)	18 (>1:512)	5 (>1:512)	28	Cure; follow-up, >6 mo
5	MV	*S. intermedius*	0.03/0.03	3.7 (0.7)	24 (1:256)	8 (1:64)	42	Cure; follow-up, >6 mo
6	AV	*S. bovis*	0.12/0.25	9.4[c] (1.5)	47 (1:128)	28 (1:64)	46	Cure; follow-up, >6 mo
7	AV	*S. bovis*	0.25/0.25	5.4 (1.1)	27 (1:128)	11 (1:64)	42	Cure; follow-up, >6 mo
8	MV	*S. bovis*	0.01/0.01	3 (1.3)	11 (1:64)	5 (1:64)	28	Relapse after 45 days

[a] MV, Mitral valve; AV, aortic valve.
[b] Measured at the time teicoplanin concentration in serum and SBA were measured.
[c] Increased dosage.

Similar SBA levels were obtained at the trough, with only two exceptions, cases 2 and 6, which had initial SBA values of 1:8 and 1:2. In the latter case, despite an immediate response to trial therapy, it was decided to increase the teicoplanin dosage from 4.7 to 9.4 mg/kg per day, thus achieving a trough SBA level of 1:64.

Cures were obtained in seven of eight cases. A relapse 45 days after teicoplanin discontinuation was observed in one patient with *Streptococcus bovis* endocarditis and echocardiographically documented valve calcification, who completed a 28-day course of antibiotic therapy. This patient was the only one of three with *Streptococcus bovis* endocarditis who had evidence of colonic disease (adenomatous polyp of the large intestine).

Enterococcal endocarditis. All isolates causing enterococcal endocarditis were susceptible to teicoplanin, and for three of four the MBC/MIC ratio was below 32 (Table 3). Pathogens were eradicated from three of the four evaluated patients. Patient 1 was a bone marrow recipient with a catheter-related right-side endocarditis. Despite a clinical response to trial treatment, inadequate SBA levels prompted us to increase the daily teicoplanin dosage from 4.8 to 7.2 mg/kg on day 10. The patient died 9 months after teicoplanin discontinuation without any evidence of relapse. In case 2, the initial daily dosage was increased from 4.7 to 7 mg/kg to achieve apparently high SBA levels; however, because of echocardiographic evidence of large vegetations, mitral valve replacement was performed on day 19. Culture of the removed valve was negative. No relapse was observed during the follow-up. Patient 3 was a patient with a 10-month history of enterococcal endocarditis who had a relapse after 42 days of ampicillin therapy. Although apparently high levels of SBA were achieved during trial therapy, another relapse was observed on day 27 after teicoplanin discontinuation. Massive calcification of the infected aortic and mitral valves was documented on surgery. The patient was cured with a successive 6-week course of ampicillin and gentamicin. Patient 4 was a man who improved on teicoplanin treatment, but intravenous netilmicin (5 mg/kg per day) was added to the antibiotic regimen on day 20 on the basis of a persistently high erythrocyte sedimentation rate and inadequate peak levels of SBA (<1:2). No relapse was observed during the 7-month follow-up.

Staphylococcal endocarditis. Nine cases of staphylococcal endocarditis were studied (Table 4). Of these, five were caused by *S. aureus* and four were caused by *Staphylococcus epidermidis*. All but one of these isolates were susceptible to oxacillin (MIC, <2 mg/ml), and none was tolerant.

Three patients with right-side infective endocarditis (cases 3, 5, and 6) were cured with teicoplanin alone. In particular, patient 3 was a 71-year-old patient with a possible infection of the transvenous pacemaker endocardial insertion sites caused by *S. aureus*. The patient improved under teicoplanin therapy and refused surgery to remove the implanted pacemaker leads. To obtain microbial eradication of this infection, a 130-day course of therapy was performed. No side

TABLE 3. Teicoplanin therapy for enterococcal endocarditis: relationship between in vitro susceptibility of the pathogen, drug and bactericidal levels in serum, and clinical outcome

Case no.	Infection site[a]	Etiology	MIC/MBC (μg/ml)	Dosage (mg/kg per day) (serum creatinine [mg/100 ml])[b]	Levels in serum (μg/ml) (SBA) at:		Days of therapy	Outcome and clinical notes
					1 h	24 h		
1	TV	*E. faecalis*	1/4	7.2[c] (0.7)	43 (1:8)	16 (1:2)	45	Cure; death after 9 mo; ANLL relapse
2	MV	*E. faecalis*	0.06/0.5	7[c] (0.9)	47 (1:128)	18 (1:32)	52	Cure; follow-up, >6 mo; MV replaced on day 19
3	MV, AV	*E. faecalis*	0.12/1	3 (0.9)	25 (1:128)	8 (1:64)	42	Relapse on day 27
4	AV	*E. faecalis*	0.06/32	5.4 (1.7)	23 (1:64)	11 (1:64)	44	Cure; netilmicin also administered Follow-up >6 mo

[a] TV, Tricuspid valve; MV, mitral valve; AV, aortic valve.
[b] Measured at the time teicoplanin concentration in serum and SBA were measured.
[c] Increased dosage.

TABLE 4. Teicoplanin therapy of staphylococcal endocarditis: relationship between in vitro susceptibility of the pathogen, drug and bactericidal levels in serum, and clinical outcome

Case no.	Infection site[a]	Etiology	MIC/MBC (μg/ml)	Dosage (mg/kg per day) (serum creatinine [mg/100 ml])[b]	Levels in serum (μg/ml) (SBA) at:		Days of therapy	Outcome and clinical notes
					1 h	24 h		
1	MV	*S. aureus*	0.25/0.25	7[c] (1)	46 (>1:512)	ND[d] (>1:512)	54	Cure; follow-up >6 mo; MV replaced on day 10; splenectomy for abscess
2	TV	*S. aureus*	0.5/8	8.8[c] (0.7)	ND (1:64)	ND (1:64)	124	Death under antibiotic therapy of aseptic pulmonary embolism despite TV removal[e]
3	RVW	*S. aureus*	0.12/0.12	7.8 (0.9)	ND (1:64)	ND (1:64)	130	Cure; follow-up, >6 mo
4	APV	*S. aureus*	0.12/2	7.8 (1)	32 (1:64)	11 (1:64)	42	Cure; follow-up, >6 mo; therapy started after valve replacement
5	AS	*S. epidermidis*	0.5/8	7.2[c] (1)	48 (1:8)	18 (<1:2)	42	Cure; follow-up, >6 mo
6	TV, AS	*S. epidermidis*	2/2	8[c] (0.8)	75 (1:4)	19 (<1:2)	28	Cure; follow-up, >6 mo
7	TV	*S. epidermidis*	1/4	14.4[c] (1)	52 (1:8)	25 (1:4)	23	Death; at autopsy, endocarditis was cured[f]
8	MPV	*S. epidermidis*[g]	0.5/8	9.2 (1.1)	66 (>1:512)	35 (1:256)	60	Cerebral embolus at day 56; death of pneumonia on day 20 after therapy
9	TV	*S. aureus*	2/4	5.7 (1.1)	34 (1:256)	8 (1:32)	42	Cure; netilmicin was also administered

[a] MV, Mitral valve; TV, tricuspid valve; RVW, right ventricular wall (pacemaker lead insertion site); APV, aortic prosthetic valve; MPV, mitral prosthetic valve; AS, atrial septum.
[b] Measured at the time teicoplanin concentration in serum and SBA were measured.
[c] Increased dosage.
[d] ND, Not determined.
[e] No response to teicoplanin alone. Rifampin, gentamicin, and erythromicin were also administered.
[f] Ceftazidime and amphotericin B were also administered; death was due to cytomegalovirus and *Aspergillus* pneumonia.
[g] Oxacillin-resistant strain.

effects were observed during this prolonged therapy, nor was any relapse observed during a 1-year follow-up. Four patients required other antibiotics in combination with teicoplanin. Oral rifampin (600 mg/day) was initiated because of persistently high erythrocyte sedimentation rate values and low SBA levels (1:4) in patient 8. Netilmicin (300 mg in two divided intravenous daily doses) was initiated when fever and pulmonary embolism recurred in patient 9. For patient 7, empiric treatment with ceftazidime and amphotericin B was added to trial therapy because of fever and profound granulocytopenia; the patient ultimately died of cytomegalovirus and *Aspergillus* pneumonia. An autopsy showed no bacteria and histological cure of the endocarditis.

Case 2 was an *S. aureus* right-side endocarditis in a drug addict, with a clinical course that had worsened on previous therapy with cefotaxime and penicillin, with a number of septic pulmonary emboli and bilateral pneumothorax and empyema. Teicoplanin as the sole therapy failed to cure the *S. aureus* bacteremia. The addition of multiple antibiotics resulted in definite fever disappearance and negative blood cultures. However, the patient experienced additional pulmonary embolic episodes. For this reason the tricuspid valve was removed on day 115, but the patient subsequently died under trial therapy because of a new episode of pulmonary embolism. Histology and culture of the removed valve failed to detect any evidence of active infection.

Autopsy examination showed fibrotic organization of the previous pulmonary embolic lesions and a recent massive aseptic embolus in the right lung.

Two additional patients required combined medical and surgical therapy. In case 1, persistent fever prompted the removal of the involved mitral valve and splenectomy for an ultrasonographically documented abscess. In case 4, trial treatment was initiated after *S. aureus* endocarditis was diagnosed at surgery in a patient with leakage of a mechanical aortic prosthesis.

Other cases of gram-positive-bacterial endocarditis. Two other cases of infective endocarditis are reported in Table 5. Patient 1 was a patient with fever, negative blood cultures, and large vegetations on the mitral valve documented with two-dimensional echocardiography. To prevent systemic emboli it was decided to replace the mitral valve before starting trial therapy. Although culture of the removed valve yielded negative results, gram-positive cocci were seen within suppurative lesions on tissue sections. Patient 2 was a bone marrow recipient with a catheter-related JK corynebacterial right-side endocarditis. Reappearance of fever during profound persistent granulocytopenia prompted us to discontinue trial therapy. On the basis of negative blood cultures, disappearance of tricuspid valve vegetations at echocardiographic examination, and positive surveillance cultures for *Aspergillus* species, empiric amphotericin B therapy was initiated, with definitive fever disappearance.

Adverse effects. Side effects attributable to trial treatment were observed in 3 (13%) of the 23 evaluated cases. One patient complained of nausea. Two other patients (patient 4, Table 3; patient 2, Table 4) on teicoplanin plus aminoglycoside therapy developed renal impairment. Serum creatinine levels rose from a pretherapy value of 0.7 mg/100 ml to a maximum of 2.1 mg/100 ml on day 95 of teicoplanin-plus-gentamicin treatment in one patient (patient 2, Table 4) who died during therapy for massive pulmonary embolism. In the other one (patient 4, Table 3), serum creatinine values rose from 1.5 mg/100 ml (pretreatment) to 4.5 mg/100 ml on day 22

TABLE 5. Teicoplanin therapy of two additional gram-positive-bacterial endocarditis cases

Case no.	Infection site[a]	Etiology	MIC/MBC (μg/ml)	Dosage (mg/kg per day) (serum creatinine [mg/100 ml])[b]	Levels in serum (μg/ml) (SBA) at:		Days of therapy	Outcome and clinical notes
					1 h	24 h		
1	MV	Unknown		6	ND[c]	ND	42	Cure; follow-up, >6 mo; trial therapy started after valve replacement
2	TV, PAW	JK corynebacteria	0.12/0.25	8.1 (0.6)	24 (1:256)	5.3 (1:64)	21	Cure; follow-up, >6 mo

[a] MV, Mitral valve; TV, tricuspid valve; PAW, posterior atrial wall.
[b] Measured at the time teicoplanin concentration in serum and SBA were measured.
[c] ND, Not determined.

of teicoplanin-plus-netilmicin therapy and decreased to 3.1 and 1.7 mg/100 ml at 2 weeks and 2 months, respectively, after antibiotic discontinuation.

DISCUSSION

During a 3-year study, we evaluated 23 cases of infective endocarditis caused by various gram-positive organisms, including those resistant to many old and new antibiotics. Several patients entered in this trial received teicoplanin dosages higher than those previously adopted. This may justify the high levels of SBA against the majority of the isolates. However, it should be stressed that in our study the SBA test was performed in broth. Since teicoplanin is a highly protein-bound agent, it is probable that the results of the SBA test would have been substantially different if corrected for protein binding (26). Bacteriological cures were obtained in 21 of 23 cases. All three patients who died during therapy or follow-up showed microbiological (Gram stain and culture) and histological documentation of the clearance of their infections at autopsy; also, valves removed from all patients during medical therapy were sterile. The duration of bacteremia after the initiation of treatment was not precisely evaluated. However, all patients (except one) for whom blood cultures were performed during treatment (including eight of nine with staphylococcal endocarditis) became abacteremic during teicoplanin therapy. Fever for more than 48 h and/or recurring during therapy was seen in only three cases, all with staphylococcal endocarditis and severe extracardiac infections. Of these, only one (patient 2 in Table 4) was bacteremic while receiving intravenous teicoplanin as the sole medical therapy.

Viridans group streptococci represent the most frequent cause of infective endocarditis (24). Like *Streptococcus bovis*, they are usually highly susceptible to penicillin, and a 28-day infusion therapy with this antibiotic is adequate for infective endocarditis caused by these organisms (27). However, a different therapy is needed for patients with proven allergies to penicillin.

In our study, successful outcomes were obtained with all six patients who completed the 6-week teicoplanin treatment. Relapse was observed in one of the two patients treated for 4 weeks.

In a recent published series, all five cases of infective endocarditis, including three prosthetic valve infections, caused by penicillin-susceptible streptococci were cured by teicoplanin therapy (25). There were two cases of natural valve endocarditis, and both were treated with intravenous teicoplanin as the sole therapy at daily dosages of 200 mg (3 mg/kg) for 30 and 38 days. Additional antibiotics for longer times were necessary for the remaining three cases with prosthetic valve infections. All of the above data seem to suggest that high doses (>7 mg/kg per day) or combined antibiotics should be used for prosthetic valve infections or for short courses (4 weeks) of therapy. Nevertheless, further studies are necessary to assess whether therapy with teicoplanin may provide the same efficacy as penicillin-based regimens for penicillin-susceptible streptococcal endocarditis.

E. faecalis endocarditis is still difficult to treat, and synergistic penicillin-aminoglycoside therapy has been recommended (18, 27). Although *E. faecalis* is usually tolerant to teicoplanin (4, 13, 23), we observed only one of four isolates for which the MBC/MIC ratio was >32. Teicoplanin plus netilmicin was required to achieve apparently adequate SBA levels against this tolerant strain. This seems to confirm the previous observation in animal models of teicoplanin-aminoglycoside in vivo synergy (20). All of the other three cases caused by nontolerant *E. faecalis* isolates were treated with teicoplanin alone. Bacteriological cures were observed in both patients treated with high doses (>7 mg/kg per day). However, right-side endocarditis in one of these could have been a more easily treatable disease than left-side infective endocarditis. For the other patient, surgery might have played a major therapeutic role. On the other hand, a relapse was documented in the patient given a trial drug dosage of 3 mg/kg per day, even though apparently adequate SBA levels (>1:64) were obtained during the therapy. The presence of massive valve calcification, which was documented during surgery, may have contributed to the failure to eradicate bacteria in this case. Glupczynski et al. (8) observed a relapse after 13 weeks in a patient with prosthetic valve infection who had been given teicoplanin at the dosage of 200 mg/kg per day for 6 weeks. Webster et al. (25) successfully used teicoplanin plus gentamicin therapy for two cases of enterococcal endocarditis, one of which was caused by a tolerant strain. The above data confirm that at present, combination therapy would be required in all situations when dealing with enterococcal endocarditis.

Recent clinical trials have shown that intravenous teicoplanin therapy at a dosage of 200 mg/day (3 mg/kg per day) is not adequate for successful treatment of severe staphylococcal infections (1). In the present study, on the basis of SBA level monitoring, teicoplanin was administered at daily dosages at least twice as high as those previously used (1, 8, 11, 14, 25). In the present series, five patients with staphylococcal endocarditis were treated with teicoplanin alone, three had right-side endocarditis, and two were treated with teicoplanin plus surgery. The location of endocarditis on the right side of the heart and surgical intervention may have favored ease of curing these patients. In addition, it should be pointed out that the other patient cured of staphylococcal endocarditis by teicoplanin and netilmicin also had right-side

endocarditis. These considerations suggest that the cases of staphylococcal endocarditis treated with teicoplanin may have been a less arduous test of therapy and that the definite assessment of teicoplanin in this situation still requires further investigation. Since no side effects were observed (except one case of nausea) in patients treated with teicoplanin alone, it may be possible to further increase the cure rate in cases of staphylococcal and, possibly, enterococcal endocarditis. In the two cases treated with an aminoglycoside combined with teicoplanin, mild signs of renal toxicity were observed. Because of the small number of these cases it was not possible to determine whether the frequency of this side effect is higher than that observed when aminoglycosides are used alone. It is prudent to monitor renal function when teicoplanin-aminoglycoside combinations are used. In conclusion, teicoplanin administered once a day at dosages of 7 to 14 mg/kg per day is well tolerated, easy to administer, and seems to be efficacious therapy for most cases of gram-positive-bacterial endocarditis.

LITERATURE CITED

1. **Calain, P., K. H. Krause, P. Vaudaux, R. Auckenthaler, D. Leew, F. Waldvogel, and B. Hirshel.** 1987. Early termination of a prospective randomized trial comparing teicoplanin and flucloxacillin for treating severe staphylococcal infections. J. Infect. Dis. **155**:187–191.
2. **Cavenaghi, L., A. Corti, and G. Cassani.** 1986. Comparison of solid phase enzyme receptor assay (SPERA) and the microbiological assay for teicoplanin. J. Hosp. Infect. **7**(Suppl. A):85–89.
3. **Chambers, H. F., and M. A. Sande.** 1984. Teicoplanin versus nafcillin and vancomycin in the treatment of experimental endocarditis caused by methicillin-susceptible or -resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **26**: 61–64.
4. **Cynamon, M. H., and P. A. Granato.** 1982. Comparison of the in vitro activities of teichomycin A_2 and vancomycin against staphylococci and enterococci. Antimicrob. Agents Chemother. **21**:504–505.
5. **Galetto, D. W., J. A. Boscia, W. D Kabasa, and D. Kaye.** 1986. Teicoplanin compared with vancomycin for treatment of experimental endocarditis due to methicillin resistant *Staphylococcus epidermidis*. J. Infect. Dis. **154**:69–75.
6. **Garvey, G. S., and H. C. Neu.** 1978. Infective endocarditis—an evolving disease. A review of endocarditis at the Columbia Presbyterian Medical Center, 1968–1973. Medicine **57**:105–127.
7. **Gilbert, B. W., R. S. Haney, F. Crawford, J. McClellan, H. A. Gallis, M. L. Johnson, and J. A. Kisslo.** 1977. Two-dimensional echocardiographic assessment of vegetative endocarditis. Circulation **55**:346–353.
8. **Glupczynski, Y., H. Lagast, P. Van Der Auwera, J. P. Thys, F. Crokaert, E. Yourassowsky, F. Meunier-Carpentier, J. Klastersky, J. P. Kains, E. Serruys-Schoutens, and J. C. Legrand.** 1986. Clinical evaluation of teicoplanin for therapy of severe infections caused by gram-positive bacteria. Antimicrob. Agents Chemother. **29**:52–57.
9. **Jadeja, L., V. Fainstein, B. LeBlanc, and G. P. Bodey.** 1983. Comparative in vitro activities of teichomycin and other antibiotics against JK diphtheroids. Antimicrob. Agents Chemother. **24**:145–146.
10. **Kaye, D.** 1985. Changing pattern of infective endocarditis. Am. J. Med. **78**(Suppl. 6B):157–162.
11. **Kosmidis, J., S. Kastanakis, and E. Kouroumalis.** 1985. Teicoplanin, a new glycopeptide antibiotic. In vitro activity pharmacokinetic studies and therapeutic efficacy in Gram-positive infections. Chemioterapia **4**(Suppl. 2):695–696.
12. **Murray, B. E., A. W. Karchmer, and R. C. Moellering.** 1980. Diphtheroid prosthetic valve endocarditis. A study of clinical features and infecting organisms. Am. J. Med. **69**:838–848.
13. **Neu, H. C., and P. Labthavikul.** 1983. In vitro activity of teichomycin compared with those of other antibiotics. Antimicrob. Agents Chemother. **24**:425–428.
14. **Pauluzzi, S., A. Del Favero, F. Menichetti, E. Baratta, M. Moretti, P. DiFilippo, M. B. Pasticci, G. R. Guerciolini, L. Patoia, and R. F. Frongillo.** 1987. Treatment of infections by staphylococci and other Gram-positive bacteria with teicoplanin. An open study. J. Antimicrob. Chemother. **20**:431–438.
15. **Robbins, M. J., R. Soeiro, W. H. Frishmar, and J. A. Strom.** 1986. Right-sided valvular endocarditis: etiology, diagnosis and an approach to therapy. Am. Heart J. **111**:128–135.
16. **Rosen, P., and D. Armstrong.** 1973. Infective endocarditis in patients treated for malignant neoplastic diseases: a post mortem study. Am. J. Clin. Pathol. **60**:241–250.
17. **Schoenknecht, F. D., L. D. Sabath, and C. Thornsberry.** 1985. Susceptibility tests: special tests, p. 1000–1008. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and H. J. Shadomy (ed.), Manual of clinical microbiology, 4th ed. American Society for Microbiology, Washington, D.C.
18. **Serra, P., C. Brandimarte, P. Martino, S. Carlone, and G. Giunchi.** 1977. Synergistic treatment of enterococcal endocarditis. In vitro and in vivo studies. Arch. Intern. Med. **137**: 1562–1567.
19. **Sheagren, J. N.** 1981. Endocarditis complicating parenteral drug abuse, p. 211–233. *In* J. S. Remington and M. N. Swartz (ed.), Current clinical topics in infectious disease, vol. 2. McGraw-Hill Book Co., New York.
20. **Sullan, P. M., M. G. Tauber, C. J. Hackbarth, and M. A. Sande.** 1985. Therapeutic efficacy of teicoplanin in experimental enterococcal endocarditis. Antimicrob. Agents Chemother. **27**:135–136.
21. **Thrupp, L. D.** 1980. Susceptibility testing of antibiotics in liquid media, p. 73–113. *In* V. Lorian (ed.), Antibiotics in laboratory medicine. The Williams & Wilkins Co., Baltimore.
22. **Varaldo, P. E., E. Debbia, and G. C. Schito.** 1983. In vitro activity of teichomycin and vancomycin alone and in combination with rifampin. Antimicrob. Agents Chemother. **23**:402–406.
23. **Verbist, L., B. Tjandramaga, B. Hendrickx, A. Van Hecken, P. Van Melle, R. Verbesselt, J. Verhaegen, and P. J. De Deschepper.** 1984. In vitro activity and human pharmacokinetics of teicoplanin. Antimicrob. Agents Chemother. **26**:881–886.
24. **Von Reyn, C. F., B. S. Levy, R. D. Arbeit, G. Friedland, and C. S. Crumpacker.** 1981. Infective endocarditis: an analysis based on strict case definition criteria. Ann. Intern. Med. **94**:505–518.
25. **Webster, A., A. P. R. Wilson, A. H. Williams, T. Treasure, and R. N. Gruneberg.** 1987. The use of a new glycopeptide antibiotic, teicoplanin, in the treatment of bacterial endocarditis. Postgrad. Med. J. **63**:621–624.
26. **Weinstein, M. P., C. A. Stratton, A. Ackley, H. B. Hawley, P. A. Robinson, B. D. Fisher, D. S. Stephens, and L. B. Reller.** 1985. Multicenter collaborative evaluation of a standardized serum bactericidal test as a prognostic indicator in infective endocarditis. Am. J. Med. **78**:262–269.
27. **Wilson, W. R., and J. E. Geraci.** 1985. Treatment of streptococcal infective endocarditis. Am. J. Med. **78**(Suppl. 6B):128–137.