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# Evaluation of Teicoplanin for Treatment of Endocarditis Caused by Gram-Positive Cocci in 20 Patients

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**Teicoplanin, a new glycopeptide antibiotic similar to vancomycin, was evaluated for the treatment of bacterial endocarditis in an open multicenter study from May 1985 to August 1987. A total of 20 patients with positive blood culture endocarditis received teicoplanin once daily as a mean intravenous injection of 7.3 mg/kg of body weight (range, 4.8 to 10.6 mg/kg); in 17 patients, teicoplanin was combined with another antibiotic, usually an aminoglycoside. The mean duration of therapy was 28 days (range, 7 to 66 days). The diagnosis of endocarditis was confirmed by echocardiography or anatomical findings in 15 patients and established on the basis of clinical manifestations plus positive blood cultures in 5 patients. The tricuspid valve was involved in 11 of the 20 patients. Isolates from blood were 12 *Staphylococcus aureus*, 1 *Staphylococcus hominis*, 1 *Micrococcus sedentarius*, 1 *Enterococcus faecalis*, 3 *Streptococcus bovis*, and 2 nongroupable *Streptococcus* sp. At the end of therapy, bacterial eradication was achieved in 17 of 20 patients (85%), and a favorable clinical outcome had occurred in 14 of 17 evaluable patients (82%). Of these 14 patients, one relapsed 4 months after the end of treatment. Thus, teicoplanin was effective in 13 of 17 patients (76%). Mean peak levels of teicoplanin in serum were lower, 23.1 ± 2.9 μg/ml, in patients who failed than in those who were cured (45.8 ± 8.4 μg/ml). Side effects occurred in 7 of 20 patients (35%), and required premature discontinuation of teicoplanin in 3 patients. These side effects were fever in three patients, rash in three patients, hearing loss in two patients, and increased serum transaminase levels in two patients. This study demonstrates the efficacy of teicoplanin in the treatment of endocarditis and the need for achieving peak levels in serum close to 40 μg/ml. Teicoplanin should now be further evaluated in endocarditis caused by gram-positive cocci by means of a controlled comparative study with standard therapy.**

Bacterial endocarditis remains a severe disease because of (i) an increased incidence of microorganisms less susceptible to beta-lactam antibiotics, such as methicillin-resistant staphylococci and aminoglycoside-resistant enterococci, and (ii) an increased frequency of prosthetic valve endocarditis. The frequency of tricuspid endocarditis in intravenous (i.v.) drug abusers is also increasing (1). Concurrently, there has been a trend to reduce the duration of in-hospital stay of patients and to make the treatment of bacterial endocarditis more acceptable to them.

Teicoplanin is a new glycopeptide antibiotic that is chemically related to vancomycin (16, 23) and has similar activity in vitro against gram-positive bacteria (11, 18, 20). However, its longer half-life gives levels in serum above the MICs for susceptible microorganisms for over 24 h after a single-dose injection (20). In the treatment of experimental endocarditis caused by various staphylococcal species (7, 19) and enterococci (17), teicoplanin compared favorably with other antibiotics used to treat endocarditis in humans. These features justified an open study to evaluate the efficacy and safety of teicoplanin for the treatment of bacterial endocarditis.

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## MATERIALS AND METHODS

**Patient enrollment.** This multicenter open study examined patients with endocarditis caused by gram-positive cocci and was conducted from May 1985 to August 1987. Patients enrolled in the trial were adults who gave informed consent. The criteria used to define endocarditis were those proposed by Von Reyn et al. (21), modified to include echocardiographic evidence of vegetations as one of the criteria for definite endocarditis. Only patients with positive blood culture endocarditis were included. Patients with a history of hypersensitivity to vancomycin, patients with renal failure, and pregnant patients were excluded.

**Teicoplanin treatment.** Teicoplanin (200-mg vials) was supplied by the Merrell Dow Research Institute. Teicoplanin was given by i.v. bolus. After a loading dose of 400 mg for the first 12 h, teicoplanin was given once daily at an initial dose of 6 mg/kg. The dose was adjusted thereafter to the levels in serum so as to maintain the peak level between 40 and 50 μg/ml and the trough level between 10 and 15 μg/ml. The duration of treatment was 30 days for streptococcal native valve endocarditis and 40 days for staphylococcal, enterococcal, or prosthetic valve endocarditis.

**Monitoring for efficacy and toxicity.** Assessment of patients included daily recording of the clinical manifestations of endocarditis, blood cultures performed before and after the onset of treatment, and weekly assessments of peripheral blood cell counts, creatinine serum, proteinuria, transami-

nases, and alkaline phosphatase serum levels. Audiometric testing was performed before, during, and after treatment whenever possible. Blood samples for determination of levels of teicoplanin in serum were collected 60 min after the i.v. injection and just before the next injection. Levels of teicoplanin in serum were measured by one of three methods: solid-phase enzyme receptor assay (11 patients), high-performance liquid chromatography assay (4 patients), or microbiological assay (1 patient). The three methods have been compared in the literature, and their results have been closely correlated (5, 10). Mean levels of teicoplanin were calculated by averaging mean values generated for each patient.

**Antimicrobial susceptibility testing.** The MICs of teicoplanin for the microorganisms isolated from blood cultures were determined by using a twofold tube macrotitration technique in cation-supplemented Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.), with an inoculum of approximately $5 \times 10^6$ organisms in log-growth phase (15). To determine MBCs, we plated 0.01-ml samples from each dilution of teicoplanin showing no turbidity after 24 h. The control sample contained approximately $5 \times 10^4$ organisms. The MBC was defined as the lowest dilution of teicoplanin giving 99.9% killing after 24 h of incubation. Detection of methicillin resistance for staphylococci was performed by plating the strain onto agar containing 10 μg of oxacillin per ml and by the agar disk diffusion procedure, using Mueller-Hinton agar and a 1-μg oxacillin disk. Heterogeneous resistance was evidenced by comparison of the diameters of the zones of inhibition observed after incubation at 37 and 30°C for 24 h (2).

**Evaluation of efficacy.** The efficacy of teicoplanin was assessed by both bacteriological and clinical criteria. Bacterial eradication was considered when the microorganism isolated from the blood before treatment could not be recovered subsequently from blood and, when available, from the valve during or after treatment. Bacterial persistence was considered when the initial microorganism was still recovered from blood or from the valve after 6 days of teicoplanin treatment. Clinical outcome was considered to be favorable when the clinical manifestations of endocarditis resolved or improved after treatment. Failure was defined as persistence or worsening of the clinical signs of infection during treatment. Relapse was defined as the reappearance of clinical signs of infection and reisolation of the causative organism after termination of treatment.

## RESULTS

**Patients and features of endocarditis.** A total of 20 patients, 11 males and 9 females, were enrolled in the study (Table 1). A predisposing factor was present in 15 of the 20 patients: intravenous drug abuse in 6, cirrhosis in 3, severe burns in 2, and an underlying cardiovascular condition in 4. One patient had an aortic Starr valve, one had a ventricular septal defect, and two had a previous history of endocarditis. One patient (no. 8) with a left-sided endocarditis had an endocardial pacemaker, which was probably not responsible for this episode of endocarditis. The portal of entry of the infecting organism was cutaneous (12 patients) or urinary, colonic, gynecologic, or dental (1 patient each).

The clinical signs of endocarditis were fever (all patients), cardiac murmur (12 patients [60%]), and embolic (8 patients [40%]), pulmonary (7 patients), systemic (1 patient), and cutaneous (1 patient) manifestations. Also present were other septic localizations (5 patients [25%]), osteoarthritis (2 patients), cellulitis (1 patient), meningitis (2 patients), and renal abscesses (1 patient). All patients had positive blood cultures. The infecting microorganisms and their susceptibilities are shown in Table 2. Methicillin resistance was detected in 2 of 12 *Staphylococcus aureus* isolates. Echocardiography showed valvular vegetations in 12 patients and an aortic insufficiency in 2 patients. Thus, the diagnosis of bacterial endocarditis was established as follows: 5 patients had probable endocarditis, with fever and positive blood cultures, combined with either a cardiac murmur or two peripheral clinical manifestations; 15 patients had a diagnosis of definite endocarditis, confirmed in 10 patients by echocardiography, in 5 patients by examination of the valve, in 4 at surgery, and in 1 at autopsy. Nine patients had left-sided endocarditis: aortic in three patients, mitral in four, and mitroaortic in two. Of the 11 patients with tricuspid endocarditis, 1 (no. 20) had an endocarditis involving both a ventricular septal defect and the tricuspid valve.

**Teicoplanin treatment.** Before starting teicoplanin treatment, six patients had received no antibiotic. Eight patients had received an inappropriate bacteriostatic treatment for a mean duration of 16 days (range, 5 to 30 days), which did not control the evolution of the endocarditis; in seven of these patients, blood cultures performed just before teicoplanin treatment was started were positive. Six patients had received a bactericidal antibiotic combination for a mean duration of 2 days (range, 1 to 4 days).

Teicoplanin was administered i.v. once daily to all 20 patients. The mean dose was 7.3 mg/kg of body weight (range, 4.8 to 10.6 mg/kg) per injection. The mean duration of teicoplanin treatment was 28 days (range, 7 to 66 days). Teicoplanin was given for more than 22 days in 14 of the 20 patients. The reasons for premature discontinuation of teicoplanin were failure of this therapeutic regimen in three patients and serious side effects in three others.

Levels of teicoplanin in serum (mean ± standard deviation) were 36.6 ± 14.0 μg/ml (58 samples) at peak and 13.6 ± 6.5 μg/ml) (63 samples) at trough in 16 patients. Peak and trough levels in serum were not strictly correlated with the daily dose of teicoplanin.

Monotherapy with teicoplanin was used in three patients with native valve endocarditis: two patients with *S. aureus* tricuspid endocarditis and one patient with *Staphylococcus hominis* mitral endocarditis. An aminoglycoside was combined with teicoplanin in 14 patients for a mean duration of 27 days (range, 3 to 66 days). In the remaining three patients, teicoplanin was combined with fosfomycin (one patient) or rifampin (two patients).

**Cardiac surgery.** Four of the patients were operated on. Two underwent valve replacement during teicoplanin treatment, on day 12 of treatment for the patient with an aortic Starr valve endocarditis and on day 26 for a patient with a native aortic valve endocarditis. Two patients underwent valve replacement at or after the end of teicoplanin treatment because of aortic insufficiency. Anatomical findings confirmed the diagnosis of bacterial endocarditis in these four patients. The valve culture grew *Micrococcus sedentarius*, the same microorganism initially isolated from the blood, in the patient with prosthetic valve endocarditis; cultures were negative in the other three patients.

**Initial course.** The bacteriological response was evaluated in all of the 20 patients. Bacterial eradication was achieved at the end of treatment in 17 patients (85%). Bacterial persistence was observed in the valve of one patient with *M. sedentarius* prosthetic valve endocarditis and in two patients with an *S. aureus* tricuspid endocarditis whose blood cul-

TABLE 1. Presentation of 20 patients with gram-positive coccal endocarditis treated with teicoplanin

| Patient no. (age [yr]) | Organism, site, means of diagnosis[a] | Wt (kg) | Serum creatinine (μM) | Teicoplanin treatment | | Teicoplanin concn in serum[b] (μg/ml) | | Replacement regimen | Valve surgery (day) | Outcome | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Dose (mg/kg per day), (duration [days]) | Combined antibiotic | Peak | Trough | | | Clinical | Bacteriological |
| With peak level of teicoplanin in serum of >30 μg/ml | | | | | | | | | | | |
| 1 (55) | *Streptococcus bovis*, mitral, C | 50 | 50 | 7.3 (23) | Netilmicin | 39.3 | 16.6 | Fucidic acid, rifampin | No | Cure | Eradication |
| 3 (20) | *Staphylococcus aureus*, tricuspid, E | 53 | 94 | 7.5 (41) | Rifampin | 40 | 13.8 | None | No | Cure | Eradication |
| 4 (18) | *Staphylococcus aureus*, tricuspid, E | 52 | 70 | 10.4 (39) | Netilmicin | 49.4 | 12.3 | None | No | Cure | Eradication |
| 6 (74) | *Enterococcus faecalis*, aortic, E, A | 61 | 114 | 10.6 (48) | Netilmicin | 56 | 28 | None | Yes (26) | Cure | Eradication |
| 7 (68) | *Staphylococcus hominis*, mitral, E | 45 | 85 | 8.9 (40) | None | 54.6 | 21.9 | None | No | Cure | Eradication |
| 8 (59) | *Streptococcus bovis*, mitral, C | 60 | 110 | 6.7 (40) | Netilmicin | 41.6 | 17.8 | None | No | Cure | Eradication |
| 13 (54) | *Staphylococcus aureus*, tricuspid, E | 92 | 80 | 6.5 (36) | None | 54 | 18.3 | None | No | Cure | Eradication |
| 17 (28) | *Staphylococcus aureus*, aortic, E, A | 61 | 95 | 6.5 (66) | Amikacin | 34.3 | 14.5 | None | Yes (62) | Cure | Eradication |
| 20 (40) | *Streptococcus mitis*, tricuspid, E | 74 | 70 | 5.4 (38) | Netilmicin | 52.6 | 9.5 | Pristinamycin | No | Cure | Eradication |
| With peak level of teicoplanin in serum of <30 μg/ml | | | | | | | | | | | |
| 2 (49) | *Micrococcus sedentarius*, aortic Starr, A | 58 | 99 | 8.6 (14) | Netilmicin | 25.8 | 17.5 | Vancomycin, amikacin, rifampin | Yes (12) | Failure | Persistence |
| 5 (26) | *Staphylococcus aureus*, tricuspid, E | 49 | 70 | 10.2 (10) | None | 20 | 7.3 | Oxacillin, netilmicin | No | NE[c] | Eradication |
| 15 (33) | *Staphylococcus aureus*, tricuspid, E | 62 | 100 | 6.4 (14) | Fosfomycin | 15.5 | 7.8 | Pefloxacin, rifampin | No | NE | Eradication |
| 16 (62) | *Staphylococcus aureus*, tricuspid, A | 49 | 97 | 8.1 (7) | Amikacin | 19.9 | 4.4 | Fosfomycin, rifampin | No | Failure, death | Persistence |
| 18 (59) | *Streptococcus sanguis*, mitroaortic, A | 76 | 80 | 7 (17) | Netilmicin | 22.5 | 9.1 | Penicillin, netilmicin | Yes (43) | NE | Eradication |
| 19 (60) | *Streptococcus bovis*, mitral, C | 89 | 106 | 6.7 (26) | Gentamicin | 23.5 | 14.9 | None | No | Relapse[d] | Eradication, then relapse in cerebrospinal fluid |
| Levels of teicoplanin in serum not determined | | | | | | | | | | | |
| 9 (57) | *Staphylococcus aureus*, mitroaortic, C | 74 | 71 | 5.4 (40) | Amikacin | ND | ND | None | No | Cure | Eradication |
| 10 (26) | *Staphylococcus aureus*, tricuspid, C | 65 | 117 | 6.1 (7) | Rifampin | ND | ND | Vancomycin, pefloxacin | No | Failure | Persistence |
| 11 (64) | *Staphylococcus aureus*, tricuspid, E | 83 | 53 | 4.8 (24) | Amikacin | ND | ND | Oxacillin | No | Cure | Eradication |
| 12 (19) | *Staphylococcus aureus*, tricuspid, E | 60 | 40 | 6.7 (23) | Netilmicin | ND | ND | None | No | Cure | Eradication |
| 14 (35) | *Staphylococcus aureus*, tricuspid, E | 63 | 90 | 6.3 (31) | Netilmicin | ND | ND | Pristinamycin | No | Cure | Eradication |

[a] C, Clinical; E, by echography; A, anatomical.
[b] Mean value of concentrations measured during teicoplanin therapy. ND, Not determined.
[c] NE, Not evaluable.
[d] Initially favorable outcome, then relapse.

TABLE 2. Infecting microorganisms and their susceptibilities in 20 patients with bacterial endocarditis treated with teicoplanin

| Microorganism | No. of cases | Teicoplanin susceptibility (μg/ml) | |
|---|---|---|---|
| | | MIC | MBC |
| *Staphylococcus aureus* | 12 | 0.25–4 (0.5[a]) | 0.25–64 (0.5[b]) |
| *Staphylococcus hominis* | 1 | 0.03 | 0.06 |
| *Micrococcus sedentarius* | 1 | 0.05 | 128 |
| *Streptococcus bovis* (group D) | 3 | 0.001, 0.007, 0.25 | 0.03, 32, 50 |
| *Enterococcus faecalis* | 1 | 0.01 | 0.01 |
| Nongroupable *Streptococcus* | 2 | 0.003, 0.003 | 12.5, 12.5 |

[a] MIC for 50% of the isolates.
[b] MBC for 50% of the isolates.

tures were still positive after 6 and 7 days, respectively, of teicoplanin treatment.

The clinical response was not evaluable in the three patients who had discontinued teicoplanin before day 23 for reasons other than failure. Of these, two patients developed fever and rash on day 10, which resolved after discontinuation of the drug. These two patients were cured by further antimicrobial therapy and were thought to have manifestations of hypersensitivity to teicoplanin. The third patient had a *Streptococcus sanguis* endocarditis and became afebrile, with negative blood cultures, on teicoplanin plus netilmicin treatment. However, fever possibly related to teicoplanin appeared on day 14, and the hemodynamic status of this patient deteriorated. On day 16, he was changed to a penicillin G-netilmicin combination for a further 18-day course and was then operated on. His valve was sterile.

A favorable clinical outcome was achieved at the end of treatment in 14 of the 17 evaluable patients (82%), and the 3 cases of bacterial persistence corresponded to the clinical failures. One patient (no. 2) was a 49-year-old male with *M. sedentarius* endocarditis involving an aortic Starr valve. Despite sterile blood cultures, persistence of fever and worsening of cardiac failure led to aortic valve replacement on day 12 of teicoplanin-plus-netilmicin treatment. At surgery, a perivalvular abscess with disinsertion of the aortic prosthesis was found. The valve culture was positive for *M. sedentarius*, which had the same susceptibility profile as did the initial strain (Table 2). The patient was treated with vancomycin combined with amikacin and rifampin and subsequently had a favorable outcome. The second patient (no. 10) was a 26-year-old i.v. drug abuser with tricuspid endocarditis caused by methicillin-susceptible *S. aureus* (MIC and MBC of teicoplanin, 0.25 and 0.5 μg/ml, respectively). Fever persisted and lung abscesses developed while he was treated with teicoplanin combined with rifampin. Blood cultures remained positive, with selection of a rifampin-resistant mutant on day 6. Treatment was changed on day 8 to vancomycin plus pefloxacin, which allowed a favorable outcome. Thus, in these two patients with failure of the teicoplanin regimen, the antimicrobial treatment was changed and cure was obtained. The third patient (no. 16) was a paraplegic 62-year-old man with nosocomial tricuspid endocarditis caused by a methicillin-resistant *S. aureus* plus pulmonary embolisms. Despite teicoplanin treatment for 7 days combined with amikacin treatment for 3 days, he had persistence of fever, deteriorating hemodynamic status, and persistence of positive blood cultures up to death on day 10. At autopsy there was evidence of tricuspid endocarditis, with a 4-cm-long well-organized thrombus appended to the tricuspid valve.

**Subsequent course.** Among the 14 patients initially considered to be cured by the teicoplanin treatment, one patient (no. 19) relapsed. He was a 69-year-old male who first presented with fever, a mitral murmur, and *Streptococcus bovis* isolated from blood cultures. At that time, he also presented with transient diplopia and inflammatory meningitis and was explored by computed tomography scan and carotid and vertebrobasilar arteriography, which could not detect any visible lesion. He was given teicoplanin for 26 days combined with gentamicin for 19 days, with a favorable clinical and bacteriological response. Colonic polyps were removed at the end of this treatment. Four months later, he developed headaches, papilledema, and bacterial meningitis, and the same strain of *Streptococcus bovis* was isolated from cerebrospinal fluid despite negative blood cultures. Further cerebral computed tomography scan and arteriography were still normal. He was then treated with vancomycin combined with rifampin for 15 days, followed by ceftriaxone plus netilmicin for 26 days, and did not relapse during a 9-month follow-up period.

**Prognostic factors.** Overall, teicoplanin treatment was associated with a favorable outcome of endocarditis without relapse in 13 of 17 evaluable patients (76%). The prognosis of patients treated with teicoplanin did not differ according to the site of infection or the type of causative microorganism. Among the evaluable patients, 7 of 9 (78%) with tricuspid endocarditis and 6 of 8 (75%) with left-sided endocarditis had a favorable outcome; 9 of 12 patients (75%) with staphylococcal (including *M. sedentarius*) endocarditis and 4 of 5 (80%) with streptococcal endocarditis had a favorable outcome. Considering only staphylococcal endocarditis, the prognosis did not appear to be different between i.v. drug addicts (one of four failed) and non-drug-addicted patients (two of eight failed). The two patients with left-sided *S. aureus* endocarditis responded favorably. Mean peak levels of teicoplanin in serum were different between the patients with favorable outcome, 45.8 ± 8.4 μg/ml ($n = 10$), and those who failed, 23.1 ± 2.9 μg/ml ($n = 3$) ($P < 0.01$). However, mean trough levels in serum were similar, 15.6 ± 6.7 and 12.3 ± 6.9 μg/ml, respectively, in the two groups.

**Adverse events.** Adverse events possibly related to teicoplanin occurred in 7 of the 20 patients (35%) (Table 3). These were fever in three patients, rash in three patients, hearing loss in two patients, and increased transaminase levels in serum in two patients. One of the two patients who experienced hearing loss was a 68-year-old female treated with teicoplanin monotherapy. She had a normal audiometric test performed when treatment was instituted and developed a 50- to 60-dB decrease in high-frequency (2,000- to 8,000-Hz) auditory threshold, recognized at the end of a 40-day course of teicoplanin. This side effect persisted 2 years later. In addition, a transient increase of serum creatinine equal to 20% of the initial value occurred in one patient (no. 8) and resolved after the end of treatment; this patient was treated with a teicoplanin-netilmicin combination. These side effects required premature discontinuation (before day 23 of teicoplanin treatment) in 3 of the 20 patients (15%).

## DISCUSSION

This study confirms that teicoplanin in combination with another antibiotic, usually an aminoglycoside, is effective for

TABLE 3. Adverse effects of teicoplanin in 7 of 20 teicoplanin-treated patients with bacterial endocarditis

| Patient no. | Adverse effects | Days after onset of teicoplanin treatment | Teicoplanin dose (mg/kg per day) | Imputability | Comments |
|---|---|---|---|---|---|
| 1 | Rash, hypereosinophilia | 13 | 7.3 | Definite[a] | Only netilmicin combined, resolution after discontinuation of both drugs on day 23 |
| 4 | Transaminase elevation | 22 | 10.4 | Possible | No change, spontaneous resolution |
| 5 | Rash, fever | 9 | 10.2 | Probable | No other antibiotic combined, resolution after teicoplanin discontinuation on day 10 |
| 7 | Hearing loss | 41 | 8.9 | Probable | No other ototoxic drug combined, no improvement |
| 15 | Rash, fever, transaminase elevation | 10 | 6.4 | Possible | Only fosfomycin combined, resolution after discontinuation of both drugs on day 14 |
| 18 | Fever | 10 | 7 | Probable | Concomitant dental abscess, resolution after discontinuation of teicoplanin on day 16 |
| 19 | Hearing loss | 25 | 6.7 | Possible | Preexisting hearing loss, partial improvement after teicoplanin discontinuation on day 26 |

[a] Recurrence of adverse effects after reintroduction of teicoplanin treatment.

treatment of bacterial endocarditis caused by gram-positive cocci. The 76% cure rate observed in this series was similar to the favorable outcome in 7 of 10 evaluable patients in the series of Webster et al. (22) and comparable to results reported by others (9, 12). This cure rate was not different from the reported 15 to 25% mortality rate for bacterial endocarditis (21). Many factors can influence the outcome of endocarditis, and they must be considered in evaluating any therapeutic regimen. The predominant factor is the occurrence of endocarditis on a native valve or a prosthetic valve. In this series, 19 of 20 patients had native valve endocarditis; therefore, the efficacy of teicoplanin cannot be extrapolated to patients with prosthetic valves. However, in the experience of Webster et al., three of four evaluable patients with prosthetic valve endocarditis were cured by teicoplanin treatment (22). Another important prognostic factor is the type of microorganism; there is a mortality rate of approximately 40% for staphylococcal endocarditis but an average of only 20% for streptococcal endocarditis (21). In our short experience, the efficacy of teicoplanin was not different in staphylococcal and streptococcal cases. However, not only the type but also the susceptibility of the microorganism must be considered (13). It is notable that the three patients with staphylococcal endocarditis who failed to respond to teicoplanin had less susceptible strains. Two had strains for which the MBC was higher than 64 μg/ml and the MBC/MIC ratio (which defines tolerance in vitro [13]) was higher than 32; in the third patient, a rifampin-resistant mutant appeared after a 6-day course of treatment despite the combination of teicoplanin and rifampin, a finding that has been reported for the combination of vancomycin and rifampin. The patient with the *Streptococcus bovis* endocarditis who relapsed (the bacterium was reisolated from cerebrospinal fluid) probably had a septic focus in contact with the meninges that could not be detected and was thought to be a septic intracranial phlebitis. The diffusion of teicoplanin and gentamicin in the central nervous system might have been insufficient to eradicate the infective microorganism from that site, whereas the endocardial site was cured. Another factor that could have favorably influenced the prognosis in this series is the high proportion of right-sided endocarditis and the high proportion of i.v. drug abusers, since this type of endocarditis is known to have a rather good prognosis and a mortality rate of approximately 10 to 15% (1). Nevertheless, the prognosis of staphylococcal endocarditis was not different between the patients with and without a history of drug addiction and between the patients with tricuspid and those with mitroaortic involvement. Further evaluation of teicoplanin in more precisely defined groups of patients, especially those with methicillin-resistant staphylococcal endocarditis, is warranted.

The dose of teicoplanin required to treat endocarditis is not well established. The experience of Calain et al. suggested that doses of higher than 200 mg/day were required to treat severe staphylococcal infections (4). These authors suggested rapid attainment of serum levels of higher than 15 μg/ml. In our series, the mean daily dose did not differ between the patients who were cured and those who failed, but the levels of teicoplanin in serum were not related to the daily dose used as reported by Calain et al. (4). Therefore, the lower peak levels in patients who fail warrant careful monitoring of the levels of teicoplanin in serum to allow adjustment of the daily dose (9). Although one should be cautious in interpreting the difference between peak levels in patients who were cured and those who failed, it appeared to us that peak levels in serum of higher than 20 μg/ml, and optimally between 40 and 50 μg/ml, should be obtained rapidly to cure endocarditis. This may require a higher loading dose of teicoplanin than the dose used in this study, with i.v. injections repeated twice daily for the first few days of treatment until the optimal peak level is achieved, as suggested by Bibler and co-workers (3).

However, use of higher doses of teicoplanin may lead to increased toxicity. Although the levels in serum were not different between the patients with adverse effects and those with good tolerance in this study, the 35% toxicity rate and 14% discontinuation rate must be emphasized. Cutaneous and febrile reactions were the most frequent effects observed, although patients with a known history of allergy to vancomycin were excluded from the study. However, the frequency of allergic cross-reactivity is not established (14). Hearing loss in patients with endocarditis has been reported by Webster et al. (22) and described in experimental studies (6). This adverse effect is probably related to the prolonged administration of teicoplanin for treatment of endocarditis, as suggested by the recognition of the effect late in the course of treatment for the two patients in this study (Table 3). However, in one patient reported by Bibler et al., this adverse effect occurred after a short course of teicoplanin (3). Therefore, teicoplanin therapy should be associated with careful monitoring of audiometric parameters, especially when administered for a long period or when combined with

an aminoglycoside. We suggest that teicoplanin not be used in patients with previous hearing disorders. On the other hand, the low renal toxicity of teicoplanin, even when combined with an aminoglycoside, in our experience is similar to that reported by other authors (3, 9, 12) and compares favorably with the renal toxicity of vancomycin (8).

In conclusion, this preliminary open study suggests that further evaluation of teicoplanin in patients with bacterial endocarditis is required to validate our conclusions. Efficacy should be determined in patients who appear to have potential indications for this drug: those with methicillin-resistant staphylococcal endocarditis or with penicillinless susceptible streptococcal endocarditis, patients with a history of beta-lactam allergy, i.v. drug abusers, and patients with poor venous access. In these patients, teicoplanin treatment should be compared with standard therapy.

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