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Efficacy of Teicoplanin in Two Dosage Regimens for Experimental Endocarditis Caused by a β-Lactamase-Producing Strain of *Enterococcus faecalis* with High-Level Resistance to Gentamicin

JOSEPH D. C. YAO, CLAUDIE THAUVIN-ELIOPOULOS,* GEORGE M. ELIOPOULOS, AND ROBERT C. MOELLERING, JR.

Department of Medicine, New England Deaconess Hospital, and Harvard Medical School, Boston, Massachusetts 02215

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Optimal therapy for the treatment of infections caused by strains of enterococci demonstrating high-level resistance to gentamicin and other aminoglycosides has not been established. The present study examined the efficacy of teicoplanin, a glycopeptide antibiotic active against gram-positive bacterial infections in various animal models, in the treatment of experimental endocarditis due to a β-lactamase-producing strain of *Enterococcus faecalis* with high-level resistance to gentamicin. Vancomycin was used as a comparative antibiotic. In the first set of experiments, both antimicrobial agents were administered by continuous intravenous infusion for 5 days at dosages which yielded comparable mean levels in serum (plus or minus the standard deviation) of 14.6 ± 4.3 μg/ml for teicoplanin and 14.3 ± 2.2 μg/ml for vancomycin. These regimens proved similarly effective in sterilizing cardiac vegetations (38 versus 50% of treated animals, respectively; $P > 0.05$). Mean (plus or minus the standard deviation) residual bacterial titers within vegetations were reduced to 3.2 ± 1.2 $\log_{10}$ CFU/g and 3.4 ± 1.7 $\log_{10}$ CFU/g, respectively. In separate experiments, the potential of teicoplanin to cure endocarditis was assessed, using two dosage regimens: (i) 30 mg/kg per day (mean level in serum, 13 μg/ml) for 10 days or (ii) 150 mg/kg per day (mean level in serum, 84 μg/ml) for 5 days. Surviving animals were sacrificed 10 days after the discontinuation of therapy. Both teicoplanin regimens were more effective than the comparative vancomycin (150 mg/kg per day) regimen: 92 versus 43% cured ($P = 0.025$) in the standard-dose group, and 82 versus 37% cured ($P = 0.015$) in the high-dose group. Results in this rat model of enterococcal endocarditis show that teicoplanin may prove useful in the treatment of serious infections due to high-level-gentamicin-resistant enterococci in humans.

Since the first report in 1979 of plasmid-mediated high-level resistance to gentamicin and other aminoglycosides in enterococci (11), organisms with such resistance have occurred worldwide and have accounted for up to 50% of the clinical enterococcal isolates at one institution (31). More recently, strains demonstrating plasmid-mediated production of β-lactamase, first encountered in 1983 (16), have been recovered in several U.S. cities (15, 19, 20; E. Rhinehart, C. Wennersten, E. Gorss, G. Eliopoulos, R. Moellering, N. Smith, and D. Goldmann, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1073, 1988). At the present time, optimal therapy of serious infections caused by strains of high-level-aminoglycoside-resistant enterococci with or without concomitant production of β-lactamase is uncertain because such isolates resist synergistic killing by combinations of aminoglycosides with cell wall-active agents. Teicoplanin, a glycopeptide antibiotic chemically related to the vancomycin-ristocetin group, is active in vitro against most gram-positive bacteria (6, 7, 17, 18, 27, 28), including high-level-gentamicin-resistant, β-lactamase-producing *Enterococcus faecalis* (21, 30). This drug has also shown promising efficacy in several animal models of endocarditis due to various gram-positive organisms (2, 4, 5, 8, 25).

The present study was undertaken to evaluate the efficacy of teicoplanin compared with that of vancomycin in the treatment of endocarditis due to a high-level-gentamicin-resistant, β-lactamase-producing clinical isolate of *E. faecalis* in a rat model. Using doses of the two drugs that yielded comparable mean levels in serum, we assessed the relative activities of these agents in reducing bacterial titers within cardiac vegetations during treatment and sought evidence of definitive cures in animals observed after discontinuation of therapy. In a final set of experiments, we examined the effectiveness of high-dose teicoplanin, which is now being investigated in humans because of treatment failures occasionally encountered with the lower doses employed in earlier clinical trials (3, 13, 14, 22, 29).

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MATERIALS AND METHODS

Test organism. *E. faecalis* HH22 used in the study is a high-level-gentamicin-resistant, β-lactamase-producing clinical isolate initially described in 1983 (16).

Testing of susceptibility to antimicrobial agents. The susceptibility of the test strain to teicoplanin and vancomycin was determined in cation-supplemented Mueller-Hinton broth (BBL Microbiology Systems, Cockeysville, Md.) by a broth macrodilution method (12), using an inoculum of 10^6 CFU/ml. The influence of serum on drug activity was examined in cation-supplemented Mueller-Hinton broth supplemented with 50% rat serum. MBCs at the 99.9% killing level were determined by the method of Pearson et al. (23). The bactericidal activity of teicoplanin against the test strain

* Corresponding author.

was also evaluated in cation-supplemented dextrose-phosphate broth (GIBCO Laboratories, Madison, Wis.) by time-kill curve methods as previously described (9). The concentrations of teicoplanin and vancomycin used in the time-kill curve studies were 15 and 80 μg/ml for both drugs, which reflected the mean levels in serum achieved in rats with the various dose regimens. Time-kill studies were also done in the presence of 50% rat serum at the same concentrations for both drugs.

Antimicrobial agents. Teicoplanin was kindly provided by Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio. Vancomycin susceptibility powder was a gift of Eli Lilly & Co., Indianapolis, Ind. Vancomycin used in the animal model was obtained from Elkins-Sinn, Inc., Cherry Hill, N.J.

Production of bacterial endocarditis. Bacterial endocarditis was established in male Sprague-Dawley rats (Taconic, Germantown, N.Y.) by the technique of Santoro and Levison (24) which we modified slightly as previously described (26). A polyethylene catheter (PE-10 Intramedic tubing) was inserted across the aortic valve via the right carotid artery. At 20 min after catheterization, 10^7 CFU of the infecting strain was injected through the catheter, which was sealed and left in place throughout the experiment. Establishment of bacterial endocarditis was ascertained by positive blood cultures drawn just before therapy was begun. With this enterococcal strain, colony counts in cardiac vegetations reached 7.9 $\log_{10}$ CFU/g at the onset of therapy. Only animals with both positive blood cultures and correct placement of the catheter across the aortic valve (as noted at autopsy) were evaluated in the study.

Antimicrobial agent therapy. Treatment was started 24 h after bacterial challenge. Antibiotics were delivered by continuous intravenous infusion via an indwelling central venous catheter inserted through the external jugular vein into the superior vena cava, as previously described (26). Infusions were carefully controlled by syringe pumps (Sage pump 352; Orion Research, Inc., Cambridge, Mass.). The following three separate sets of experiments were performed.

(i) Five-day therapy study. Antibiotic doses were chosen to achieve levels in serum in rats comparable to mean concentrations in serum attainable in humans treated with standard doses of antibiotics. Animals were assigned to one of the following three groups: teicoplanin (30 mg/kg per day), vancomycin (150 mg/kg per day), or an untreated control group. Therapy was continued for 5 days. Animals were sacrificed 3 h after discontinuation of vancomycin infusion and 24 h after discontinuation of teicoplanin infusion. These time intervals, reflecting differences in the pharmacokinetics of the two agents, were chosen to ensure that the levels of antibiotics in serum had fallen to one-fourth or less of the MIC of each drug in rat serum.

(ii) Relapse study (standard-dose teicoplanin). Animals received doses of teicoplanin and vancomycin as indicated above but were treated for 10 days and then observed for 10 more days after discontinuation of therapy. At that point, survivors were sacrificed.

(iii) Relapse study (high-dose teicoplanin). Since teicoplanin has been administered to a limited number of human subjects in doses to achieve peak and trough concentrations in serum of approximately 300 and 40 μg/ml, respectively (Israel Rios, Merrell Dow Research Institute, Cincinnati, Ohio, personal communication), we delivered teicoplanin at doses of 150 mg/kg per day to achieve mean concentrations in serum of approximately 80 μg/ml. Because of favorable results observed with the 10-day treatment regimen described above, this study was designed with a shorter duration of therapy. Animals receiving teicoplanin were treated for 5 days and then observed for 11 days after discontinuation of therapy, while animals receiving vancomycin were treated for 6 days and then observed for 10 days before sacrifice. This schedule ensured comparable durations of effective drug levels in serum in the two groups because of differences in the elimination half-lives of vancomycin (0.75 h) and teicoplanin (4.0 h) established in our model.

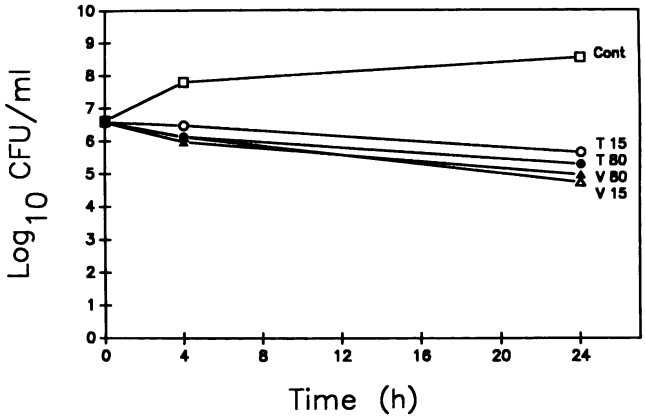

FIG. 1. Time-kill curves of teicoplanin and vancomycin against *E. faecalis* HH22. The concentrations of teicoplanin (T) and vancomycin (V) used were 15 μg/ml (T 15, V 15) and 80 μg/ml (T 80, V 80). Cont, Control.

Monitoring of therapy and outcome. On day 3 of therapy, drug levels in serum were measured, using an agar well diffusion bioassay technique (1) with *Bacillus subtilis* ATCC 6633 (Difco Laboratories, Detroit, Mich.) as the test organism. Standard curves were constructed with known concentrations of antibiotic diluted in pooled rat serum.

At the time of sacrifice, aortic vegetations were aseptically excised, weighed, homogenized, serially diluted in sterile saline, and plated to determine bacterial colony counts. The lower limit of detection by this method was 2.3 $\log_{10}$ CFU/g of vegetation. For the relapse experiments, only animals which had completed therapy and died on or after the second (vancomycin) or third (teicoplanin) day after discontinuation of therapy were included in the study.

Statistical evaluation. The chi-square test with the Yates correction was used to evaluate nominal data such as animal survival and valve sterility. Differences in bacterial titers within vegetations among controls and treatment groups were assessed by analysis of variance and *t* test corrected for multiple comparisons with the Bonferroni adjustment.

RESULTS

In vitro susceptibility studies. MICs and MBCs for *E. faecalis* HH22 in cation-supplemented Mueller-Hinton broth were 0.06 and 125 μg of teicoplanin per ml and 1 and >125 μg of vancomycin per ml, respectively. The presence of 50% rat serum increased the MIC and MBC of teicoplanin to 2 and 125 μg/ml and the MIC and MBC of vancomycin to 4 and >125 μg/ml, respectively. By time-kill methods, both teicoplanin and vancomycin failed to exhibit bactericidal activity against *E. faecalis* HH22, decreasing colony counts by only ca. 1 $\log_{10}$ CFU/ml at 24 h of incubation (Fig. 1). Similar results were obtained for both drugs in the presence of 50% rat serum (data not shown).

Experimental endocarditis. (i) Five-day therapy study. Re-

TABLE 1. Outcome of therapy in experimental enterococcal endocarditis

Regimen	Level in serum (mean ± SD; μg/ml)	No. of survivors/ no. treated (%)	No. of sterile valves/ no. of valves examined (%)	Bacterial titer in vegetation (mean ± SD; $\log_{10}$ CFU/g)
Control		6/9 (67)	0/6 (0)	8.7 ± 2.0
Teicoplanin	14.6 ± 4.3	15/18 (83)	6/16[a] (38)	3.2 ± 1.2[b]
Vancomycin	14.3 ± 2.2	4/5 (80)	2/4 (50)	3.4 ± 1.7[b]

[a] One rat died 2 h before scheduled sacrifice and was included in analysis.
[b] $P < 0.05$, compared with control.

sults of the 5-day therapy study are shown in Table 1. In both treated groups, mean levels of the drugs in serum were similar. Although there was no statistically significant difference in survival between treated and control animals, residual bacterial titers in cardiac vegetations were substantially lower and sterile valves were more frequent in treated animals than in controls ($P < 0.05$). Teicoplanin and vancomycin regimens were similar in sterilizing valves (38 versus 50%, $P > 0.05$) or in reducing bacterial titers in vegetations to 3.2 ± 1.2 versus 3.4 ± 1.7 $\log_{10}$ CFU/g, respectively.

(ii) Relapse studies. The results of relapse studies are shown in Table 2. Both dosage regimens of teicoplanin proved to be more effective than the vancomycin regimen in curing endocarditis. Ten days of treatment with comparable doses of teicoplanin and vancomycin cured 92 and 43% of the animals, respectively ($P = 0.025$). Likewise, with the short-course regimens, teicoplanin at high doses was superior to vancomycin in sterilizing valves (82 versus 37%, $P = 0.015$). Of the high-dose-teicoplanin-treated animals which died with culture-negative valves, three of four animals died on the third day of posttreatment observation. Therefore, an analysis of the results on the basis of animals surviving at least 5 days (30 times the serum half-life of teicoplanin) was undertaken. This yielded results comparable to those described above, with sterile valves in 10 of 13 (77%) teicoplanin-treated animals and 6 of 18 (33%) vancomycin-treated animals ($P < 0.05$).

DISCUSSION

The emergence of enterococci demonstrating high-level resistance to gentamicin and other aminoglycosides has provided the impetus to search for alternative bactericidal regimens for treatment of endocarditis caused by such strains. Previous work in our laboratory with this rat model has shown that ampicillin-sulbactam or daptomycin, used without concomitant aminoglycosides, resulted in cure (i.e., freedom from relapse during a posttreatment observation period) in approximately one-half of the animals receiving 10 days of therapy (10). Despite the fact that glycopeptide antibiotics generally exhibit poor bactericidal activity against enterococci when studied by both time-kill methods and determination of MBCs, teicoplanin as a single agent has shown evidence of in vivo activity against *E. faecalis* in rabbit (25) and rat (M. T. Hessen, P. G. Pitsakis, and M. E. Levison, 28th ICAAC, abstr. no. 365, 1988) endocarditis models. Sullam et al. (25), using a rabbit model of endocarditis due to an *E. faecalis* strain (teicoplanin MIC and MBC were 1 and >64 μg/ml, respectively), showed a reduction in vegetation bacterial titers to 3.57 $\log_{10}$ CFU/g in teicoplanin-treated animals compared with that of control animals (6.50 $\log_{10}$ CFU/g). Similarly, Hessen et al. (28th ICAAC) demonstrated in a rat enterococcal endocarditis model that five of five animals treated for 10 days with teicoplanin had sterile vegetations, while the drug was only bacteriostatic in vitro against the infecting strain of *E. faecalis* (MIC and MBC were 1.56 and >50 μg/ml, respectively).

The first phase of this study in which animals were sacrificed immediately after 5 days of therapy confirmed the in vivo activity of teicoplanin. However, because of the relatively long half-life of this drug in rats and its high degree of in vitro activity against *E. faecalis* HH22 (MIC, 0.06 μg/ml), it became apparent that the true therapeutic potential of this drug required assessment in a model which permitted the examination of animals for evidence of relapse well beyond discontinuation of the drug. This was accomplished in subsequent experiments which demonstrated that 10 days of therapy with teicoplanin at a dosage achieving mean levels in serum of approximately 15 μg/ml or 5 days of treatment with mean levels in serum of approximately 80 μg/ml resulted in cures of 92 and 82% of the animals, respectively. In designing these experiments, we attempted to eliminate the possibility that a carry-over of small amounts of residual teicoplanin would lead spuriously to the appearance of greater efficacy of the drug. On the basis of calculations involving drug elimination during observation periods and dilutional factors in preparing and plating valve tissue homogenate, the possibility of significant antibiotic carry-over appears to be extremely remote, even among the animals dying 72 h after discontinuation of therapy. Favorable results were observed with teicoplanin even when animals dying with sterile vegetations up to 5 days after drug discontinuation are excluded (this period represents 30 times the serum elimination half-life of teicoplanin in rats).

Given the poor bactericidal activity of teicoplanin against the test strain used in this study, as determined by MBC and time-kill techniques, we cannot readily explain the promising results observed here. This work provides justification for further studies of teicoplanin in the treatment of experimental endocarditis to examine additional strains and perhaps in other models of infection with different dosage regimens.

TABLE 2. Outcome of therapy in relapse model of experimental enterococcal endocarditis

Regimen	Standard-dose teicoplanin		High-dose teicoplanin	
	Level in serum (mean ± SD; μg/ml)	No. of sterile valves/ no. of valves examined (%)	Level in serum (mean ± SD; μg/ml)	No. of sterile valves/ no. of valves examined (%)
Teicoplanin[a]	13.2 ± 3.1	11/12 (92)[b]	84.2 ± 18.2	14/17 (82)[b]
Vancomycin[c]	15.2 ± 4.8	6/14 (43)	16.6 ± 4.7	7/19 (37)

[a] Standard dose, 30 mg/kg per day; high dose, 150 mg/kg per day.
[b] $P < 0.03$, compared with vancomycin-treated group.
[c] Vancomycin, 150 mg/kg per day in both experiments.

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