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Therapeutic Efficacy of Teicoplanin in Experimental Enterococcal Endocarditis

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The antimicrobial activities of teicoplanin and ampicillin, alone and in combination with gentamicin, were compared in experimental *Streptococcus faecalis* endocarditis. Bacterial titers in vegetations of rabbits treated with teicoplanin were significantly lower than those of untreated controls ($P < 0.01$) and were equivalent to titers in ampicillin-treated animals. Gentamicin increased the activities of both drugs to a comparable degree.

Enterococcal endocarditis continues to represent a major therapeutic challenge. Successful treatment often requires the prolonged use of multidrug regimens that are potentially toxic. With the emergence of enterococcal strains resistant to the synergistic effect of some antibiotic combinations, such as streptomycin and penicillin, treatment options have become further limited (1, 3–6). Recent studies have demonstrated that teicoplanin (theicomycin) has antimicrobial activity in vitro against many strains of *Streptococcus faecalis* (2, 9). Moreover, the combination of teicoplanin with an aminoglycoside is synergistic against the majority of strains tested. These results suggest that teicoplanin may have activity in vivo against enterococci. To assess this possibility, we evaluated the antimicrobial properties of teicoplanin in a rabbit model of enterococcal endocarditis.

Assays of antimicrobial sensitivities were performed by standard broth dilution techniques (10). The MICs and MBCs for teicoplanin, ampicillin, and gentamicin were 1 and >64 μg/ml, 1 and 4 μg/ml, and 16 and 64 μg/ml, respectively. Nonbacterial thrombotic endocarditis was established in 68 New Zealand rabbits (2 to 3 kg) by placement of a sterile polyethylene catheter across the aortic valve (7). Twenty-four hours later, 2×10^7 CFU of *S. faecalis* strain 122 were injected through a peripheral vein. To determine the vegetation bacterial titers at the onset of therapy, five animals were sacrificed 12 h after inoculation. The remaining 63 animals were randomized to one of five groups: teicoplanin (12.5 mg/kg every 12 h [q12h] intravenously, 14 animals); teicoplanin (12.5 mg/kg q12h intravenously) in combination with gentamicin (3 mg/kg q6h intramuscularly, 17 animals); ampicillin (100 mg/kg q6h intramuscularly, 9 animals); ampicillin in combination with gentamicin (100 mg/kg and 3 mg/kg q6h intramuscularly, 16 animals); or no therapy (7 animals). Peak antibiotic concentrations in serum were measured 1 h after drug administration. Trough concentrations of ampicillin and gentamicin were assayed 6 h after drug administration, whereas trough levels of teicoplanin were obtained 12 h after dosing. A strain of *Bacillus globigii* was used to measure ampicillin concentrations. A strain of *Staphylococcus epidermidis* (ATCC 27626) was used to measure teicoplanin and gentamicin concentrations. For samples obtained from animals receiving combination therapy, ampicillin and gentamicin were inactivated by penicillinase (Difco Laboratories) and cellulose phosphate, respectively (8). The drug concentrations in serum (mean ± standard deviation) of teicoplanin 1 and 12 h after drug administration were 36.2 ± 21.6 and 4.7 ± 2.4 μg/ml. Peak and trough concentrations of ampicillin in serum were 61.7 ± 24.9 μg/ml and 0.7 ± 2.0 μg/ml; for animals receiving gentamicin the peak and trough antimicrobial concentrations in serum were 6.7 ± 2.2 μg/ml and 0.5 ± 0.4 μg/ml (Table 1).

After 4 days of therapy, surviving rabbits were sacrificed. The aortic valves were excised aseptically, weighed, and homogenized in a tissue grinder. Serial 10-fold dilutions of the homogenate were made in saline and plated onto blood agar. Colony counts were performed after 48 h of incubation at 35°C and expressed as the mean $\log_{10}$ (± standard deviation) CFU per gram of vegetation. Animals that died during therapy were refrigerated at 5°C within 6 h of death until time of necropsy. Vegetations from these animals were processed as described above.

Twelve hours after inoculation the bacterial titers in the infected aortic valves (mean $\log_{10}$ ± standard deviation) were 6.50 ± 1.00 CFU/g (Table 2). After 4 days, titers had risen to 9.25 ± 0.13 CFU/g in untreated controls. Therapy with teicoplanin alone significantly inhibited bacterial growth in the valves (mean $\log_{10}$ titer, 3.57 ± 2.58 CFU/g; $P < 0.05$ compared with controls at day 4) to a degree comparable to therapy with ampicillin (mean $\log_{10}$ titer, 4.90 ± 0.92 CFU/g). Titers in animals treated with either ampicillin or teicoplanin did not differ significantly from those in animals at the onset of therapy ($P > 0.1$). However, combination therapy with teicoplanin and gentamicin significantly reduced the titers. The mean $\log_{10}$ titer for this treatment group, 1.37 ± 1.87 CFU/g of infected valve, was significantly lower than titersat the onset of therapy and titers in untreated controls ($P < 0.001$). Moreover, this regimen was as effective as the

TABLE 1. Antibiotic regimens and corresponding drug concentrations in serum 1, 6, or 12 h after drug administration

Antimicrobial agent	Dosage[a]	Mean serum concn ± SD (μg/ml) at:		
		1 h	6 h	12 h
Ampicillin	100 mg/kg q6h i.m.	61.7 ± 24.9	0.7 ± 2.0	—[b]
Gentamicin	3 mg/kg q6h i.m.	6.7 ± 2.2	0.5 ± 0.4	—[b]
Teicoplanin	12.5 mg/kg q12h i.v.	36.2 ± 21.6	—[b]	4.7 ± 2.4

[a] i.m., Intramuscularly; i.v., intravenously.
[b] —, Not done.

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TABLE 2. Effect of antimicrobial therapy on the number of bacteria per gram of vegetation

Treatment group	Titer (mean ± SD $\log_{10}$ CFU/g)
Control (12 h[a] after infection)	6.50 ± 1.00
Control (4 days after infection)	9.25 ± 0.13
Ampicillin	4.90 ± 0.92[b]
Teicoplanin	3.57 ± 2.58[b]
Ampicillin and gentamicin	2.63 ± 1.56[b,c]
Teicoplanin and gentamicin	1.37 ± 1.87[b,c]

[a] Time at which therapy was initiated.
[b] $P < 0.01$ compared with controls after 4 days.
[c] $P < 0.01$ compared with controls after 12 h.

combination of ampicillin and gentamicin (mean $\log_{10}$ titer, 2.63 ± 1.56 CFU/g; $P > 0.1$).

Thus, teicoplanin alone was comparable to ampicillin in its ability to inhibit the growth of *S. faecalis* within cardiac vegetations. When combined with gentamicin, teicoplanin demonstrated significant bactericidal activity. These results suggest that teicoplanin may be a useful alternative in the therapy of enterococcal infections when given in combination with gentamicin. Further evaluation of its clinical efficacy and possible toxicity should be considered.

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