

Comparative In Vitro Activities of Teichomycin and Vancomycin Alone and in Combination with Rifampin and Aminoglycosides Against Staphylococci and Enterococci

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The activity of teichomycin A₂ was compared with that of vancomycin in vitro against clinical isolates of staphylococci and enterococci. Teichomycin A₂ was more active than vancomycin against all isolates tested. Synergistic studies also demonstrated that teichomycin A₂ combined with rifampin is more active than vancomycin combined with rifampin against *Staphylococcus aureus* and *Staphylococcus epidermidis* isolates. Teichomycin A₂, either singly or in combination with an aminoglycoside, was more active against *Streptococcus faecalis* isolates.

Teichomycin A₂, a glycopeptide antibiotic, resembles vancomycin in its spectrum of activity and its mode of action, which is via inhibition of cell wall synthesis (8). There is a need for additional agents which are effective for the therapy of patients with serious staphylococcal infections, particularly when methicillin-resistant strains are responsible; there is also a need for additional agents for serious enterococcal diseases (2, 3, 9, 10).

The present study examines the in vitro activity of teichomycin A₂ against clinical isolates of *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), *Staphylococcus epidermidis*, and *Streptococcus faecalis*. The in vitro interactions of teichomycin A₂ and rifampin were compared with those of vancomycin and rifampin against *S. aureus*, *S. epidermidis*, and *S. faecalis* strains. In addition, the activity of vancomycin combined with aminoglycosides was compared with that of teichomycin A₂ combined with aminoglycosides in vitro against *S. faecalis* isolates.

MATERIALS AND METHODS

Thirty-two *S. aureus* strains (10 methicillin-susceptible isolates from patients with endocarditis, 10 methicillin-resistant isolates from patients with endocarditis, and 12 methicillin-resistant isolates from patients with localized infections such as wound, skin, eye, and ear infections), 10 *S. epidermidis* strains isolated from patients with endocarditis and osteomyelitis, and 10 *S. faecalis* strains isolated from patients with endocarditis or septicemia were studied. The methicillin-resistant *S. aureus* isolates were kindly provided by Dennis Schaberg, University of Michigan, Ann Arbor, and Charles Zierdt, National Institutes of Health, Bethesda, Md. All organisms were maintained on blood agar plates throughout the course of this study. The *S. aureus* (methicillin susceptible and methicillin resistant) and *S. epidermidis* isolates were identified by standard microbiological techniques. *S. faecalis* isolates were identified with bile esculin and arginine hydrolysis and growth at 45°C and in 6.5% NaCl.

The following reference standard antibiotics were supplied by the indicated manufacturers and dissolved according to

their instructions: rifampin, CIBA Pharmaceutical Co.; vancomycin hydrochloride, tobramycin, and streptomycin sulfate, Eli Lilly & Co.; gentamicin sulfate, Schering Corp.; and teichomycin A₂, Dow Chemical Co. Rifampin concentrations ranged from 0.25 to 0.0019 µg/ml, vancomycin and teichomycin A₂ concentrations ranged from 40 to 0.078 µg/ml, and aminoglycoside concentrations ranged from 400 to 1.56 µg/ml.

In vitro antibiotic susceptibility and synergy studies were performed by the microtiter checkerboard dilution system (1, 7). Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) was used for overnight broth cultures and dilution assays for *S. aureus* and *S. faecalis*. Brain heart infusion broth was used for *S. epidermidis* cultures and dilution assays. Overnight broth cultures were adjusted to 5×10^6 organisms per ml for a standard inoculum. MICs and MBCs of rifampin combined with vancomycin or teichomycin were determined for all strains. In addition, vancomycin and teichomycin combined with streptomycin, gentamicin, or tobramycin were tested against all *S. faecalis* isolates.

The MIC was defined as the lowest concentration of antibiotic(s) which allowed no visible growth of the organism in the microtiter plate after 18 h of incubation at 37°C for 18 to 24 h. The MBC was defined as the lowest concentration of antibiotic(s) which allowed no growth or ≤ 10 colonies of the organism after plating 10 µl of solution from each well and reincubation at 37°C for 18 to 24 h.

Drug combinations were considered synergistic if the MIC or MBC occurred at one-fourth or less of the MIC or MBC of each individual drug.

RESULTS AND DISCUSSION

The MICs and MBCs of rifampin, vancomycin, and teichomycin A₂ against staphylococcal and enterococcal isolates are shown in Table 1. Teichomycin A₂ was more active than vancomycin in the in vitro antibiotic susceptibility tests against *S. aureus*, *S. epidermidis*, and *S. faecalis*. There was no significant difference between the antibiotic susceptibilities of methicillin-resistant and -susceptible *S. aureus* isolates to rifampin, vancomycin, and teichomycin A₂.

The bacteriostatic and bactericidal synergy studies, in which vancomycin was compared with teichomycin A₂

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TABLE 1. Antimicrobial susceptibilities of staphylococci and enterococci

Organism (no. of strains)	Concn ($\mu\text{g/ml}$) range of:					
	Rifampin		Vancomycin		Teichomycin A ₂	
	MIC	MBC	MIC	MBC	MIC	MBC
<i>S. aureus</i>						
Methicillin susceptible (32)	0.0078–0.0312	0.0156–0.0312	1.25–2.5	1.25–5.0	0.078–0.625	0.156–1.25
Methicillin resistant (22)	0.0078–0.0312	0.0156–0.0312	1.25–2.5	1.25–5.0	0.156–1.25	0.312–2.5
<i>S. epidermidis</i>	0.0078–0.0312	0.0156–0.0625	2.5–10	2.5–20	0.625–2.5	0.625–2.5
<i>S. faecalis</i>	>0.25	>0.25	2.5–5.0	5–>40	0.312–1.75	6.25–50

TABLE 2. Synergy studies of staphylococci and enterococci

Organism	% Antibiotic combinations resulting in bacteriostatic/bactericidal synergy							
	Vancomycin plus:				Teichomycin A ₂ plus:			
	Rifampin	Streptomycin	Gentamicin	Tobramycin	Rifampin	Streptomycin	Gentamicin	Tobramycin
<i>S. aureus</i>								
Methicillin susceptible	0/20				70/100			
Methicillin resistant	4/33				50/68			
<i>S. epidermidis</i>	10/40				40/60			
<i>S. faecalis</i>	0/0	20/40	20/80	30/70	0/40	30/60	70/90	80/100

combined with rifampin or aminoglycosides in vitro against staphylococcal and enterococcal isolates, respectively, are shown in Table 2. Teichomycin A₂ and rifampin exhibited better bacteriostatic and bactericidal synergistic activities than did vancomycin and rifampin against all staphylococcal isolates. Teichomycin A₂ and aminoglycoside combinations also produced higher bacteriostatic and bactericidal synergistic activities than did vancomycin combined with an aminoglycoside against *S. faecalis* isolates.

Teichomycin A₂ has been tested in vitro against a wide spectrum of gram-positive organisms (4, 5, 8, 11). In one study, of 25 strains each of *S. aureus* and *S. epidermidis*, teichomycin A₂ had an activity similar to that of vancomycin (4). Teichomycin A₂ has shown significantly greater activity than vancomycin against the 24 enterococci tested (4). In another study of 130 staphylococci, 132 streptococci, and other gram-positive rods (i.e., clostridia, propionibacteria, and group JK organisms), teichomycin A₂ was found to be more active than vancomycin in vitro (11). The in vitro interaction of teichomycin A₂ combined with rifampin against isolates of staphylococci, streptococci, and anaerobic bacteria has been studied. Teichomycin A₂ and vancomycin have shown similar in vitro interactions with rifampin in combination tests (7). A more recent study also demonstrated that teichomycin A₂ is highly active against methicillin-resistant *S. aureus* strains but less active than vancomycin against *S. epidermidis* strains (5).

On the basis of previous in vitro studies and the present study, teichomycin A₂ seems to be more active in vitro than vancomycin against staphylococcal and enterococcal isolates. Teichomycin A₂ is a potentially useful antibiotic agent when used either singly or in combination with rifampin in the treatment of serious infections caused by *S. aureus*, including methicillin-resistant strains and *S. epidermidis*. In the treatment of severe infections caused by *S. faecalis*, teichomycin A₂ may prove to be useful either singly or in combination with aminoglycosides. Further clinical studies

are needed to determine the efficacy and toxicity of teichomycin A₂.

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