

## In Vitro Activity of Teichomycin and Vancomycin Alone and in Combination with Rifampin

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The antibacterial activity of teichomycin, a glycopeptide antibiotic similar to vancomycin, has been evaluated *in vitro* and compared with that of vancomycin. Test strains included 130 staphylococci and 132 streptococci, with representatives of the major currently recognized species or groups, and lesser numbers of clostridia, propionibacteria, and group JK bacteria. Teichomycin was found to be more active than vancomycin. Its minimum inhibitory concentration (MIC) was two- to fourfold lower than that of vancomycin with staphylococci and anaerobic bacteria, and two- to eightfold lower with streptococci. No significant differences were observed with group JK bacteria. For most strains tested, minimum bactericidal concentrations (MBCs) of both teichomycin and vancomycin either equalled or exceeded by twofold the respective MICs. Higher MBC-to-MIC ratios were obtained for enterococci and pneumococci with both antibiotics. Both teichomycin and vancomycin showed similar *in vitro* interactions with rifampin in combination tests. Neither antagonism nor (with very few exceptions) synergism occurred.

Teichomycin (originally called teichomycin A<sub>2</sub>) is a bactericidal antibiotic recently obtained from *Actinoplanes teichomyceticus* (3, 21). It is related to the glycopeptide group of antibiotics, whose major member is vancomycin, and also resembles the latter drug in the mode of inhibiting cell wall synthesis in gram-positive organisms (24).

The aim of this study was to assess the *in vitro* antibacterial activity of teichomycin and to compare it with vancomycin. Moreover, since several reports have recently emphasized the successful treatment of staphylococcal endocarditis with a combination of vancomycin and rifampin (2, 11, 14, 20), the *in vitro* interactions of teichomycin and rifampin and those of vancomycin and rifampin were also studied and compared.

The strains used in this study largely included conventional bacterial targets of vancomycin such as staphylococci and streptococci. Representatives of the major currently recognized species or groups of both organisms were tested. In addition, we investigated some strains of pathogens which have been reported to be susceptible to vancomycin, such as *Clostridium perfringens* (23) and *Propionibacterium acnes* (29), or for which vancomycin has even been suggested as the drug of choice, such as *Clostridium difficile* (16, 25) and group JK bacteria (13, 22). *C. difficile* has been clearly implicated as the causative agent of antimicrobial agent-associated pseudomembranous colitis (4, 12).

Group JK bacteria, which are provisionally still defined as corynebacteria although their taxonomic position is not yet clear, may cause severe infections, mainly in compromised hosts, and display multiple resistance to antibiotics as a distinguishing feature (13, 22).

### MATERIALS AND METHODS

**Bacterial strains.** A total of 130 staphylococci, 132 streptococci, 8 group JK bacteria, and 11 anaerobic bacteria were studied.

Most staphylococci were isolated from clinical material recently processed in our Institute's diagnostic laboratory. Their identification was performed by evaluating their lytic activity patterns (27, 28) and by other conventional tests (17). These isolates included 43 strains of *Staphylococcus aureus*, 19 strains of *S. epidermidis*, and from 3 to 9 representatives of each of the other currently recognized human species (17). In addition, 13 strains from two staphylococcal species of animal origin (*Staphylococcus hyicus* and *Staphylococcus intermedius*) were used. The latter strains were from our Institute's collection. Methicillin susceptibility of the staphylococcal isolates was determined by agar diffusion on plates of Mueller-Hinton agar (Difco Laboratories, Detroit, Mich.) supplemented with 5% NaCl, using commercial disks containing 5 µg of the antibiotic (1).

All streptococci were clinical isolates. The great majority (98 strains) were of group D. Nine isolates belonged to *Streptococcus pneumoniae*, and from 3 to 6 strains belonged to each of groups A, B, C, F, and G. Strains of *S. pneumoniae* group A and group D were identified by conventional laboratory methods (10). All group D isolates used were found to belong to

enterococcal species, based on the 6.5% NaCl tolerance test (9). The strains of the remaining groups were identified with the Streptex kit (Wellcome Research Laboratories, Beckenham, England).

Group JK bacteria were isolated from clinical specimens and identified on the basis of their peculiar multiple antibiotic resistance and the biochemical characteristics described by Riley et al. (22).

Anaerobic bacteria included five strains of *C. difficile*, three of *C. perfringens*, and three of *P. acnes*, all isolated from clinical specimens and identified by established procedures (14).

**Antibiotics.** Standard reference powders of teichomycin and rifampin were supplied by Gruppe Lepetit S.p.A., Milan, Italy; vancomycin was obtained as a commercial sample from Eli Lilly & Co., Indianapolis, Inc. Standard stock solutions of each antibiotic were prepared according to the manufacturer's instructions, stored at  $-70^{\circ}\text{C}$ , and thawed immediately before use.

**Susceptibility tests.** Minimum inhibitory concentrations (MICs) were determined by the agar dilution method (30). The test medium was Mueller-Hinton agar for staphylococci, enterococci, and group JK bacteria; the same medium supplemented with defibrinated horse blood (5%) was used for streptococci other than group D; and Schaedler agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with vitamin  $\text{K}_1$  (10  $\mu\text{g}/\text{ml}$ ) and defibrinated sheep blood (5%) was used for anaerobes. From serial twofold dilutions of teichomycin or vancomycin, test plates were prepared in which antibiotic concentrations ranged from 0.025 to 12.8  $\mu\text{g}/\text{ml}$ . Test plates without antibiotics were used as controls. The inoculum suspensions were prepared from 6-h broth cultures and adjusted so as to obtain a concentration of approximately  $10^7$  CFU/ml. Inoculation of test plates was carried out with a multipoint inoculator (model A 400; Denley, Billingshurst, England) delivering 1  $\mu\text{l}$  of bacterial suspension per spot. The inoculated plates were allowed to stand until the inoculum spots were completely absorbed and were then incubated at  $35^{\circ}\text{C}$  for 20 h. For anaerobic bacteria, incubation was carried out in an anaerobic glove box (model 1024; Forma Scientific, Marietta, Ohio). The MIC was read as the lowest antibiotic concentration which showed no visible growth. With both teichomycin and vancomycin, an MIC of  $\leq 6.4$   $\mu\text{g}/\text{ml}$  was regarded as indicating susceptibility.

Minimum bactericidal concentrations (MBCs) were determined by standard procedures (26). Serial twofold broth dilutions of teichomycin and vancomycin (1 ml per tube) were prepared; concentrations up to 102  $\mu\text{g}/\text{ml}$  were assayed. The media used were Mueller-Hinton broth (Difco) for staphylococci, enterococci, and group JK bacteria; a 1:1 mixture of Mueller-Hinton broth and Todd-Hewitt broth (Oxoid Ltd., Basingstoke, England) for non-group D streptococci; and Schaedler broth (BBL) with vitamin  $\text{K}_1$  (0.1  $\mu\text{g}/\text{ml}$ ) for anaerobes. One milliliter of the inoculum suspension (adjusted so as to contain ca.  $10^6$  CFU/ml) was added to each test tube. The tubes were incubated at  $35^{\circ}\text{C}$  for 20 h. For anaerobic bacteria, the anaerobic incubator mentioned above was used. One hundred microliters (10 samples of 10  $\mu\text{l}$ ) was drawn with a calibrated loop from the tubes showing no growth and streaked on the surface of plates containing brain heart infusion agar (Difco) with 5% defibrinated horse blood

(for aerobic bacteria) or Schaedler agar with 10  $\mu\text{g}$  of vitamin  $\text{K}_1$  per ml and 5% defibrinated sheep blood (for anaerobes). These plates were incubated at  $35^{\circ}\text{C}$  for 48 h under aerobic or anaerobic conditions, respectively. The MBC was read as the lowest antibiotic concentration which gave no visible growth in the subculture.

**Antibiotic combinations.** Combinations of teichomycin or vancomycin with rifampin were assessed by a standard checkerboard agar dilution method (18). The test media, inoculation, incubation, and reading were as described above for MIC testing. Antibiotic interactions were interpreted as follows: Synergism, when the MIC of both drugs was at least one-fourth of the MIC of each drug alone. Antagonism, when inhibition occurred at concentrations exceeding the MIC of either drug.

## RESULTS

**MIC tests.** All strains tested were susceptible to both teichomycin and vancomycin. The MIC defined as the threshold of susceptibility (6.4  $\mu\text{g}/\text{ml}$  for both antibiotics) was recorded for one isolate (belonging to *Staphylococcus xylosum*) with teichomycin and for four isolates (one belonging to *S. epidermidis*, one to *C. perfringens*, and two to enterococci) with vancomycin. Lower MICs of both antibiotics were recorded for all other strains.

For the great majority of isolates tested, the MIC of teichomycin was found to be lower than that of vancomycin. The MIC range and the MICs that were inhibitory to 50 and 90% of the organisms tested are shown in Tables 1 through 3.

With most *Staphylococcus* isolates, the MIC of teichomycin was two- to fourfold lower than that of vancomycin. The greater activity of teichomycin was apparent both in the total number of isolates and in the individual species (Table 1). The only exception was *S. xylosum*, for which an opposite behavior was recorded, with the MIC of teichomycin inhibitory to 50% of strains being twofold greater than that of vancomycin. Table 1 also shows that, for individual species as well as for total staphylococci, MICs of teichomycin were usually distributed over a wider range than those of vancomycin. In addition, the MICs of teichomycin inhibitory to both 50 and 90% of the strains of the individual staphylococcal species displayed a greater variability than those of vancomycin. Of the staphylococci tested, 24% were found to be methicillin resistant. No significant difference in the degree of in vitro susceptibility to either teichomycin or vancomycin emerged between methicillin-sensitive and methicillin-resistant isolates.

Usually, both teichomycin and vancomycin proved more active against streptococci (particularly non-group D strains) than against staphylococci. Differences similar or greater than

TABLE 1. Susceptibility of 130 *Staphylococcus* isolates to teichomycin and vancomycin

Identification <sup>a</sup>	No. of strains	MIC ( $\mu\text{g/ml}$ ) of teichomycin <sup>b</sup>			MIC ( $\mu\text{g/ml}$ ) of vancomycin <sup>b</sup>		
		Range	50%	90%	Range	50%	90%
MS <i>S. aureus</i>	29	0.4-1.6	0.8	1.6	0.8-3.2	1.6	3.2
MR <i>S. aureus</i>	14	0.4-1.6	0.8	1.6	1.6-3.2	1.6	3.2
<i>S. capitis</i>	8	0.4-1.6	0.8	0.8	1.6-3.2	3.2	3.2
<i>S. cohnii</i>	5	1.6-3.2	1.6	3.2	1.6-3.2	3.2	3.2
<i>S. epidermidis</i>	19	0.4-3.2	0.8	1.6	1.6-6.4	3.2	3.2
<i>S. haemolyticus</i>	6	0.8-3.2	1.6	1.6	0.8-3.2	3.2	3.2
<i>S. hominis</i>	8	0.2-1.6	0.8	1.6	0.8-3.2	1.6	3.2
<i>S. saprophyticus</i>	8	0.8-3.2	1.6	3.2	1.6-3.2	3.2	3.2
<i>S. simulans</i>	8	0.4-1.6	0.4	0.8	All 1.6	1.6	1.6
<i>S. warneri</i>	3	1.6-3.2	3.2	3.2	All 3.2	3.2	3.2
<i>S. xylosus</i>	9	1.6-6.4	3.2	3.2	1.6-3.2	1.6	3.2
<i>S. hyicus</i>	6	0.8-3.2	1.6	3.2	1.6-3.2	3.2	3.2
<i>S. intermedius</i>	7	0.4-0.8	0.8	0.8	0.8-1.6	1.6	1.6
Total or avg	130	0.2-6.4	0.8	3.2	0.8-6.4	3.2	3.2

<sup>a</sup> MS, methicillin susceptible; MR, methicillin resistant.

<sup>b</sup> 50% and 90%, MIC inhibiting 50 and 90% of strains, respectively.

those recorded between the two drugs for staphylococci were seen for most *Streptococcus* isolates (MICs of teichomycin were two- to eightfold lower than those of vancomycin). Moreover, for some streptococcal groups, MICs of teichomycin also appeared to be distributed over a wider range than those of vancomycin (Table 2).

For the eight strains of *Clostridium* and one strain of *P. acnes*, the MICs of teichomycin were found to be two- to fourfold lower than those of vancomycin. Equal MICs of both drugs were observed for the two remaining propionibacteria (Table 3).

Significant differences were not observed in the activities of teichomycin and vancomycin against group JK bacteria, as confirmed by the identical MIC range and MICs inhibitory to 50 and 90% of strains exhibited by the two antibiotics (Table 3).

**MBC tests.** MBC was determined for 36 isolates, selected so that at least one strain of each species was tested.

For most isolates, MBCs of both teichomycin and vancomycin either equalled or exceeded by twofold the respective MICs. MBC-to-MIC ratios higher than 2 were recorded for enterococci, pneumococci, and the *C. perfringens* strain tested. For the latter, an MBC-to-MIC ratio equal to 8 was obtained with vancomycin, whereas no difference between MBC and MIC occurred with teichomycin. For the three *S. pneumoniae* strains tested, MBC-to-MIC ratios ranged from 4 to 16 with teichomycin and from 4 to 8 with vancomycin. The highest MBC-to-MIC ratios were obtained for enterococci, for which vancomycin was not fully bactericidal even at the highest concentration tested (102.4  $\mu\text{g/ml}$ ) for four strains out of five, and an MBC-to-MIC ratio as high as 64 was obtained for the remaining strain. With teichomycin, MBC-to-MIC ratios were equal to 64 for three isolates and to 4 for two isolates.

**Combination tests.** Combinations of teichomycin or vancomycin with rifampin were assayed for a total of 86 strains. These included 60

TABLE 2. Susceptibility of 132 *Streptococcus* isolates to teichomycin and vancomycin

Identification	No. of strains	MIC ( $\mu\text{g/ml}$ ) of teichomycin <sup>a</sup>			MIC ( $\mu\text{g/ml}$ ) of vancomycin <sup>b</sup>		
		Range	50%	90%	Range	50%	90%
Group A	6	0.05-0.1	0.1	0.1	All 0.4	0.4	0.4
Group B	6	0.05-0.2	0.1	0.2	All 0.4	0.4	0.4
Group C	5	0.1-0.2	0.2	0.2	0.2-0.4	0.2	0.4
Group D	98	0.2-1.6	0.4	0.8	0.8-6.4	1.6	3.2
Group F	3	0.1-0.2	0.1	0.2	All 0.8	0.8	0.8
Group G	5	0.05-0.2	0.1	0.2	0.2-0.8	0.4	0.8
<i>S. pneumoniae</i>	9	0.05-0.2	0.05	0.1	0.2-0.8	0.4	0.8
Total or avg	132	0.05-1.6	0.2	0.8	0.2-6.4	1.6	3.2

<sup>a</sup> 50% and 90%, MIC inhibiting 50 and 90% of strains, respectively.

TABLE 3. Susceptibility of 8 isolates of group JK bacteria and 11 isolates of anaerobic bacteria to teichomycin and vancomycin

Identification	No. of strains	MIC ( $\mu\text{g/ml}$ ) of teichomycin <sup>a</sup>			MIC ( $\mu\text{g/ml}$ ) of vancomycin <sup>a</sup>		
		Range	50%	90%	Range	50%	90%
Group JK	8	0.4-0.8	0.4	0.8	0.4-0.8	0.4	0.8
<i>C. difficile</i>	5	0.4-0.8	0.8	0.8	0.8-3.2	1.6	3.2
<i>C. perfringens</i>	3	0.8-3.2	0.8	3.2	1.6-6.4	3.2	6.4
<i>P. acnes</i>	3	0.8-1.6	0.8	1.6	0.8-1.6	1.6	1.6

<sup>a</sup> 50% and 90%, MIC inhibiting 50 and 90% of strains, respectively.

staphylococci (MIC of rifampin,  $\leq 0.02$   $\mu\text{g/ml}$ ), 18 streptococci (MIC of rifampin,  $\leq 0.16$   $\mu\text{g/ml}$ ), and 8 anaerobic bacteria (MIC of rifampin,  $\leq 0.08$   $\mu\text{g/ml}$ ). At least two representatives of each species or group were used. No group JK isolate was tested as all strains were resistant to rifampin (MIC  $> 6.4$   $\mu\text{g/ml}$ ).

The major findings obtained can be summarized as follows. (i) There were no significant differences between the in vitro interaction of teichomycin and rifampin and that of vancomycin and rifampin; (ii) antagonism did not occur; (iii) indifference was the prevalent response; (iv) synergism was a rare event, only observed for two staphylococcal isolates (one of *S. aureus* and one of *S. hominis*) with the teichomycin plus rifampin combination and for one isolate (the same *S. aureus* strain as above) with the vancomycin plus rifampin combination; (v) differences from species to species were not significant.

### DISCUSSION

The development of new antibiotics such as teichomycin from the vancomycin group may be of special importance today. In fact, renewed attention is currently being focused on vancomycin after years when it was virtually unused because of its toxicity and obligatory intravenous administration. A number of recent reports have emphasized the great utility of vancomycin, alone or in combination with other antibiotics, in severe and life-threatening infections (6, 7, 11, 15) and its special efficacy against dangerous and multiply resistant newly recognized pathogens such as *C. difficile*, which responds to oral administration in pseudomembranous colitis (16, 25), or group JK bacteria.

In this study, teichomycin has proved to be more inhibiting in vitro than vancomycin against the great majority of the strains tested. In another recent study (8), carried out by a different procedure and with many fewer strains, similar differences in the in vitro activity of teichomycin and vancomycin were reported for enterococci, whereas less marked differences than those reported here were obtained for staphylococci. For most isolates tested here, a greater activity

of teichomycin was confirmed in the MBC tests. Also, for enterococci, for which a marked disparity between inhibiting and killing activity was observed (consistent with the tendency of these organisms to behave as tolerant to many bactericidal antibiotics [26]), lower MBC-to-MIC ratios were obtained with teichomycin than with vancomycin. Altogether, the greater in vitro activity of teichomycin appears to be particularly significant in light of the results of early in vivo studies on this drug. Compared with vancomycin, it can be administered intramuscularly, has lower toxicity, and gives higher and more persistent serum levels in animals as well as in human volunteers (5; V. Arioli, personal communication).

The lack of both antagonism and synergism appears to be the main aspect of our in vitro investigation of the combinations of teichomycin and vancomycin with rifampin. In the absence of antagonism, the lack of synergism does not seem to be in contrast with the reported efficacy of combined therapy with vancomycin and rifampin (2, 11, 20). The excellent entry of rifampin into phagocytic leukocytes (19) and suppression by vancomycin of the resurgence of rifampin-resistant mutants might well explain (as also suggested by others [31]) the therapeutic efficacy of this antimicrobial combination in the absence of a really synergistic drug interaction. The present findings show that the interaction of teichomycin and rifampin in vitro is similar to that of vancomycin and rifampin. Further in vivo studies are indicated to elucidate the possible advantages of teichomycin over vancomycin in combined administration with rifampin.

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