

In Vitro Activities of Vancomycin and Teicoplanin against Coagulase-Negative Staphylococci Isolated from Neutropenic Patients

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This study reports the in vitro activities of vancomycin and teicoplanin against 185 coagulase-negative staphylococcal strains isolated from 80 neutropenic patients who received different antibiotic treatments. All strains were susceptible to vancomycin: MICs for 50 and 90% of strains tested were 2 and 4 mg/liter, respectively. Teicoplanin was less active, and MICs displayed a wider range. For only teicoplanin was there a correlation between resistance and previous treatment. At the 4- and 32-mg/liter breakpoint levels, only 20% of the strains isolated from patients without glycopeptide treatment were intermediate or resistant, whereas 49.2% of the strains from patients who had received vancomycin or teicoplanin or both were intermediate or resistant.

Vancomycin and teicoplanin are glycopeptide antibiotics active against gram-positive bacteria. Teicoplanin interferes with cell wall biosynthesis by inhibiting polymerization of peptidoglycan, a mode of action very similar to that of vancomycin.

Staphylococci and especially coagulase-negative staphylococci are some of the most common infecting organisms in neutropenic patients; many such patients receive teicoplanin or vancomycin as empirical treatment. So far, there have been few observations reported concerning isolation of teicoplanin-resistant coagulase-negative staphylococci from patients treated with glycopeptides. This study reports the activities of teicoplanin and vancomycin against 185 coagulase-negative staphylococcal strains isolated from 80 neutropenic patients during a period of 1 year.

A total of 92 investigations were conducted on 80 patients admitted to the Hematology Department for acute leukemia from May 1988 to June 1989. Sixty-eight patients were investigated once, and twelve were studied twice. Sixty-two patients were hospitalized for induction remission treatment or bone marrow transplantation, and thirty were hospitalized for control of complications during remission. The distribution of patients according to antibiotic treatment was as follows: 37 had received no treatment with glycopeptides during the previous 3 months, 12 received vancomycin per os (125 mg six times per day) for intestinal decontamination, 29 received vancomycin per os (intestinal decontamination) and vancomycin intravenously (i.v.) (30 mg/kg of body weight per day), 4 received vancomycin per os (intestinal decontamination) and teicoplanin i.v. (7 mg/kg per day), 7 received only vancomycin i.v., and 3 received only teicoplanin i.v. Bacteriological surveillance was done with nose, throat, and stool cultures at least once weekly. Clinical specimens (blood, catheter, sputum, etc.) were taken for suspected infection when fever occurred.

Of the 185 strains of coagulase-negative staphylococci tested, 65 were isolated from blood, 20 were isolated from intravascular catheters, 42 were isolated from stool, 50 were

isolated from the throat, and 8 were isolated from miscellaneous sites. For septicemia (two or more positive blood cultures), only one strain per patient was used; moreover, only one strain was tested when the same strain was found in different specimens on the same day. The identities of all strains were determined by a positive catalase test and a negative coagulase test (slide test) (Staphaurex; Wellcome Burrough, Paris, France) and (for blood and catheter cultures) by a commercially available test (API Staph). All the strains of coagulase-negative staphylococci for which MICs were >16 mg/liter were reidentified at the API Research Laboratory (La Balme les Grottes, France) with the API ATB 32 Staph.

Antibiotics for susceptibility testing were obtained as standard powders as follows: vancomycin, Eli Lilly, Saint-Cloud, France; and teicoplanin, Merrell Dow, Bourgoin, France. The MICs were determined by the agar dilution method, using serial twofold dilutions ranging from 64 to 0.12 mg of antimicrobial agent per liter in Mueller-Hinton agar (Diagnostics Pasteur). The inoculum was prepared by diluting an overnight broth culture in such a way that each spot of broth delivered by the multipoint inoculator contained 10^4 to 10^5 CFU (13). Plates were examined after 24 h of incubation at 37°C. *Staphylococcus aureus* ATCC 25923 was included as a control in each test.

Table 1 shows the comparative activities of teicoplanin and vancomycin against the 185 strains of coagulase-negative staphylococci. On the basis of the MIC breakpoints recommended by the National Committee for Clinical Laboratory Standards for vancomycin (11) (susceptible, <4 mg/liter; intermediate, 8 to 16 mg/liter; and resistant, >32 mg/liter), our results clearly show that all the strains were susceptible to vancomycin, while the MICs of teicoplanin showed a wide range of values, with 41% of strains in the intermediate or resistant categories. Of five strains for which the vancomycin MIC was 4 mg/liter, the teicoplanin MICs were 32 mg/liter for three and 16 mg/liter for two. The teicoplanin-intermediate and -resistant coagulase-negative staphylococci were identified as *S. epidermidis* (86.5%), *S. hominis* (2.7%), and *Staphylococcus* spp. (13.5%).

Tables 2 and 3 show the distributions of vancomycin and

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TABLE 1. Comparative in vitro activities of vancomycin and teicoplanin against 185 isolates of coagulase-negative staphylococci

Antibiotic	No. of strains inhibited by the following concn (mg/liter):						MIC (mg/liter) ^a		
	0.5	1	2	4	8	16	32	50%	90%
Vancomycin	2	38	140	5				2	2
Teicoplanin	2	8	34	65	27	43	6	4	16

^a 50% and 90%, MIC for 50 and 90% of strains tested, respectively.

teicoplanin MICs according to the different patient populations. For vancomycin, there was no significant difference between the different populations of patients, as opposed to differences with teicoplanin. At the 4- and 32-mg/liter breakpoints, only 20% of the strains isolated from patients without glycopeptide treatment (group 1) were intermediate or resistant, whereas 45.8% of strains isolated from patients who had received oral vancomycin (group 2), 58.3% of strains isolated from patients who received i.v. vancomycin or teicoplanin (group 3), and 48.3% of strains isolated from patients who had received oral decontamination and i.v. teicoplanin or vancomycin (group 4) were intermediate or resistant. Statistical analysis by the chi-square test showed significant differences between the study groups: $P < 0.01$ between groups 1 and 2, $P = 0.02$ between groups 1 and 3, and $P < 0.001$ between groups 1 and 4. There was no apparent difference due to differences in strain origin.

Our results are in agreement with those of others (3, 4, 8, 14), who have shown that vancomycin inhibits 100% of coagulase-negative staphylococci at a concentration of 4 mg/liter while teicoplanin tends to be less active. The resistance of *S. haemolyticus* to teicoplanin is known (1, 12, 16), but few researchers (6) have reported resistance of other coagulase-negative staphylococcal species and, particularly, *S. epidermidis*. Moore and Speller (9) reported that only 42% of coagulase-negative staphylococci isolated from patients with endocarditis were inhibited by 4 mg of teicoplanin per liter, and our results are similar. Recently, Goldstein et al. (F. Goldstein, A. Coutrot, and J. F. Acar, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 698, 1989) reported that 25% of coagulase-negative staphylococci isolated in their hospital were intermediate or resistant to teicoplanin and *S. epidermidis* represented 74% of their strains.

It is apparent that differences exist in MICs according to techniques used (2, 7). Bauernfeind and Petermuller (2) found that the MIC for *S. epidermidis* could be increased by up to 32-fold by using a solid medium, but recently Felmingham et al. (5) showed that MICs determined by a mac-

TABLE 2. MICs of vancomycin against 185 coagulase-negative staphylococcal strains according to previous treatment

Treatment ^a (no. of strains)	No. of strains inhibited by the following concn (mg/liter):			
	0.5	1	2	4
None (53)	1	13	39	
Vanco per os (48)		10	36	2
Vanco per os + i.v. (50)		5	42	3
Vanco per os + Teico i.v. (10)			10	
Vanco i.v. (19)	1	8	10	
Teico i.v. (5)		2	3	

^a Vanco, Vancomycin; Teico, teicoplanin.

TABLE 3. MICs of teicoplanin against 185 coagulase-negative staphylococcal strains according to previous treatment

Treatment ^a (no. of strains)	No. of strains inhibited by the following concn (mg/liter):						
	0.5	1	2	4	8	16	32
None (53)		4	17	21	7	3	1
Vanco per os (48)	1	3	9	13	8	13	1
Vanco per os + i.v. (50)		1	4	22	3	19	1
Vanco per os + Teico i.v. (10)			1	3	2	1	3
Vanco i.v. (19)	1		3	5	4	6	
Teico i.v. (51)				1	3	1	

^a Vanco, Vancomycin; Teico, teicoplanin.

rodilution technique with an inoculum of 10^4 CFU/ml are very similar to those determined in agar. Thus, it seems unlikely that differences in technique are responsible for the higher MICs of teicoplanin found in our study.

Kaatz and Seo (G. W. Kaatz and S. M. Seo, 29th ICAAC, abstr. no. 1197, 1989) and Wilson et al. (16) reported cases of teicoplanin-resistant staphylococci isolated from patients treated with glycopeptides. Our results confirm that it is extremely difficult to select for resistance to vancomycin in vitro, whereas the selection of stepwise resistance has been reported for teicoplanin (10, 15), with high MICs (>256 mg/liter).

In conclusion, this study suggests that teicoplanin is less active in vitro than vancomycin against many coagulase-negative staphylococci and that previous treatment by a glycopeptide may be responsible for the emergence of teicoplanin resistance. For neutropenic patients who present with a coagulase-negative staphylococcal infection and who have previously been treated with a glycopeptide, a clinical study should be performed to determine the in vivo incidence of these results.

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