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In Vitro Activities of Eight Macrolide Antibiotics and RP-59500 (Quinupristin-Dalfopristin) against Viridans Group Streptococci Isolated from Blood of Neutropenic Cancer Patients

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From January 1988 to December 1994, 66 consecutive blood culture isolates of viridans group streptococci collected from febrile neutropenic cancer patients were tested for antimicrobial susceptibilities by the agar dilution method. The antibiotics studied were erythromycin, clarithromycin, roxithromycin, dirithromycin, azithromycin, josamycin, diacetyl-midecamycin, spiramycin, and quinupristin-dalfopristin. A total of 26 (39.4%) strains were resistant to erythromycin with an MIC range of 0.5 to >128 μg/ml. The strains were classified into three groups according to their penicillin susceptibility: 42 (63.6%) were susceptible, 8 (12.1%) were intermediately resistant, and 16 (24.3%) were highly resistant. The percentages of erythromycin-resistant strains in each group were 23.8, 62.5, and 68.8%, respectively. *Streptococcus mitis* was the species most frequently isolated (83.3%) and showed the highest rates of penicillin (40%) and erythromycin (43.6%) resistance. MICs of all macrolide antibiotics tested and of quinupristin-dalfopristin were higher for penicillin-resistant strains than for penicillin-susceptible strains. All macrolide antibiotics tested had cross-resistance to erythromycin, which was not observed with quinupristin-dalfopristin. Our study shows a high rate of macrolide resistance among viridans group streptococci isolated from blood samples of neutropenic cancer patients, especially those infected with penicillin-resistant strains. These findings make macrolides unsuitable prophylactic agents against viridans group streptococcal bacteremia in this patient population.

In recent years, viridans group streptococci have become a major cause of bacteremia in neutropenic cancer patients (2, 4, 5, 9, 11). They can cause serious complications, including encephalopathy, shock, and adult respiratory distress syndrome, which cause appreciable mortality (10, 11, 13, 18, 27, 29, 32). As a result, different prophylactic regimens to prevent these serious infections have recently been studied.

In some institutions, prophylactic penicillin has been successfully used to decrease the incidence of viridans group streptococcal bacteremia in neutropenic cancer patients (14). However, the emergence of bacteremia due to penicillin-resistant viridans group streptococci has recently been observed (1a, 4, 6, 7, 17, 22, 25, 31). In addition, the development of bacteremia due to resistant strains in neutropenic cancer patients who received penicillin prophylaxis has been documented, suggesting that resistance to penicillin might limit its utility as a prophylactic agent (4, 17).

Thus, there is an urgent need for alternative antimicrobial agents which can be used for prophylaxis, especially in institutions where β-lactam-resistant streptococci are frequently isolated. Although data are limited, the macrolides alone (roxithromycin) or in combination with other antimicrobial agents (fluoroquinolones, rifampin, or minocycline) have recently been suggested as an alternative for the prevention of streptococcal infections in neutropenic cancer patients (16, 19, 22, 23).

The aim of this study was to determine the susceptibilities of 66 consecutive viridans group streptococcus strains isolated from the blood of neutropenic cancer patients to eight macrolide antibiotics and quinupristin-dalfopristin, which could prove to be useful to prevent these infections.

(This study was partially presented at the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., September 1995 [1].)

MATERIALS AND METHODS

Organisms. A total of 66 strains of viridans group streptococci isolated consecutively from blood samples taken between January 1988 and December 1994 in the Hospital "Prínceps d'Espanya" (Barcelona, Spain) were tested for antimicrobial susceptibilities. These strains were recovered from adult neutropenic cancer patients (<500 granulocytes per mm^3). Only one isolate per patient was tested. Norfloxacin was administered orally (400 mg twice daily) as prophylaxis. No other antibacterial prophylaxis was given. Blood cultures were performed, from 1988 to 1989, by the Roche Septi-Chek system (Hoffman-La Roche, Inc., Nutley, N.J.). From 1990 on, the samples were inoculated into BACTEC bottles and tested on a BACTEC NR 860 instrument (Johnston Laboratories, Inc., Towson, Md.).

Alpha-hemolytic and nonhemolytic streptococci were identified and speciated according to standard methods (12, 24). Colony morphology was evaluated, and pure cultures were tested for production of acid from trehalose, sorbitol, lactose, mannitol, sucrose, inulin, raffinose, glycerol, arabinose, maltose, and sorbose. Isolates were additionally tested for reactions in esculin agar and bile esculin agar, growth in 6.5% sodium chloride broth, ammonia production from arginine, pyruvate utilization, sodium hippurate hydrolysis, and hydrolysis of starch. We used the taxonomy and nomenclature proposed by Coykendall (8) and advocated by Facklam and Washington (12), which include five species or groups: *Streptococcus mitis*, *Streptococcus sanguis*, *Streptococcus anginosus* (or "*Streptococcus milleri*"), *Streptococcus salivarius*, and *Streptococcus mutans*. Although an accurate identification by only phenotypic methods is troublesome, this simplified scheme provides enough microbiological information to be used for clinical purposes.

Antimicrobial agents. The following antibiotics were tested: penicillin (C.E.P.A., S.L., Madrid, Spain), erythromycin (Abbott Laboratories, North Chicago, Ill.), clarithromycin (Abbott Laboratories), roxithromycin (Roussel Ibérica S.A., Madrid, Spain), dirithromycin (Eli Lilly & Co., Indianapolis, Ind.), azithromycin (Pfizer Laboratories, Madrid, Spain), josamycin (Ferrer Internacional S.A., Barcelona, Spain), diacetyl-midecamycin (Menarini Laboratories, Barce-

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lona, Spain), spiramycin (Rhône-Poulenc Rorer, Antony, France), and quinupristin-dalfopristin (Rhône-Poulenc Rorer).

Susceptibility testing. MICs were determined by the agar dilution method as recommended by the National Committee for Clinical Laboratory Standards (20). The inoculum was prepared by suspending some colonies from an overnight blood agar culture in sterile 0.9% saline and adjusting the turbidity to the 0.5 McFarland standard (ca. 10^8 CFU/ml). The suspension was further diluted to provide a final concentration of bacteria of 10^4 CFU per ml per spot, which was delivered by a Steers replicator onto Mueller-Hinton agar plates supplemented with 5% defibrinated horse blood and appropriate concentrations of the antibiotics. The plates were incubated in 5% CO_2 at 35°C for 20 to 24 h. The MIC was defined as the lowest concentration of antibiotic that inhibits visible growth. Strains were classified for penicillin and erythromycin susceptibility according to the National Committee for Clinical Laboratory Standards criteria (21), as follows: a determination of susceptibility to penicillin requires an MIC of 0.12 μg/ml or less, intermediate resistance to penicillin requires an MIC of 0.25 to 2 μg/ml, high resistance to penicillin requires an MIC of at least 4 μg/ml, susceptibility to erythromycin requires an MIC of 0.25 μg/ml or less, intermediate resistance to erythromycin requires an MIC of 0.5 μg/ml, and high resistance to erythromycin requires an MIC of at least 1 μg/ml. *Streptococcus pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 29213 were used for the quality control. The *S. aureus* control strain tested in CO_2 gave MICs for macrolide antibiotics within the range expected for ambient air.

RESULTS

The distribution of viridans group streptococci for species isolated was 55 *S. mitis* strains, 6 *S. salivarius* strains, 2 *S. sanguis* strains, 2 *S. anginosus* strains, and 1 *S. mutans* strain.

The isolates were classified into three groups according to their penicillin susceptibility: 42 (63.6%) were susceptible, 8 (12.1%) were intermediately resistant, and 16 (24.3%) were highly resistant. There were statistically significant differences in the percentages of erythromycin resistance, according to the new National Committee for Clinical Laboratory Standards criterion (MIC, ≥0.5 μg/ml) (21), for each group susceptible to penicillin, which were as follows: 23.8% of penicillin-susceptible strains, 62.5% of intermediately resistant strains, and 68.8% of highly resistant strains (chi-square test, 11.83; $P < 0.01$).

Among the 66 viridans group streptococci studied, only 40 (60.6%) strains were susceptible to erythromycin (MIC, ≤0.25 μg/ml), 3 (4.5%) strains were intermediately resistant to erythromycin (MIC, 0.5 μg/ml), and 23 (34.8%) were resistant to erythromycin (MIC, 1 to >128 μg/ml). The MIC at which 50% of the isolates were inhibited (MIC_{50}) and the MIC_{90} of erythromycin were 0.06 and >128 μg/ml, respectively. Eleven of 23 erythromycin-resistant strains showed a high level of resistance (MIC, >128 μg/ml). The MICs for the remaining 12 resistant strains ranged from 1 to 4 μg/ml. Among the 23 erythromycin-resistant strains, 13 were also resistant to clindamycin (MIC, ≥1 μg/ml), 5 were intermediately resistant to clindamycin, (MIC, 0.5 μg/ml), and 5 were susceptible to clindamycin (MIC, ≤0.25 μg/ml).

The ranges of MICs and the MIC_{50} and MIC_{90} of each of the tested antibiotics for the test strains, with the strains grouped according to susceptibility to penicillin and erythromycin, are presented in Tables 1 and 2. As is shown, the in vitro activities of the 14-membered lactone ring compounds—clarithromycin, roxithromycin, and dirithromycin—and the 15-membered ring macrolide—azithromycin—tested decreased in correlation with the in vitro activities of penicillin. MIC_{90}s of these macrolide antibiotics tested were >128 μg/ml for the strains intermediately resistant and highly resistant to penicillin. The MIC of clarithromycin was 1 dilution lower than that of erythromycin. Roxithromycin and azithromycin showed in vitro activities similar to that of erythromycin. Dirithromycin had slightly lower in vitro activity than erythromycin. The in vitro activities of the 16-membered compounds tested—josamycin, diacetylmidecamycin, and spiramycin—were less affected by the degrees of penicillin resistance of viridans group streptococci. Quinupristin-dalfopristin was the most active drug tested against penicillin-resistant strains (MIC_{50}, 1 μg/ml; MIC_{90}, 8 μg/ml).

TABLE 1. In vitro activities of eight macrolide antibiotics and quinupristin-dalfopristin against viridans group streptococci isolated from blood samples of neutropenic cancer patients

Antibiotic	Type of viridans group streptococcus[a]	MIC (μg/ml)		
		Range	50%	90%
Erythromycin	S	≤0.01–>128	0.03	2
	IR	≤0.01–>128	0.5	>128
	HR	≤0.01–>128	2	>128
Clarithromycin	S	≤0.01–>128	≤0.01	1
	IR	≤0.01–>128	0.25	>128
	HR	≤0.01–>128	1	>128
Roxithromycin	S	≤0.01–>128	0.03	2
	IR	≤0.01–>128	0.5	>128
	HR	≤0.01–>128	2	>128
Dirithromycin	S	0.03–>128	0.12	4
	IR	0.06–>128	1	>128
	HR	0.06–>128	4	>128
Azithromycin	S	≤0.01–>128	0.06	2
	IR	0.03–>128	0.5	>128
	HR	0.03–>128	2	>128
Josamycin	S	0.03–>128	0.06	0.5
	IR	0.03–>128	0.06	>128
	HR	0.03–>128	0.12	>128
Diacetyl-midecamycin	S	0.06–>32	0.25	1
	IR	0.12–>32	0.5	>32
	HR	0.12–>32	0.5	>32
Spiramycin	S	≤0.01–>128	0.06	0.5
	IR	0.03–>128	0.06	>128
	HR	0.03–>128	0.12	>128
Quinupristin-dalfopristin	S	0.25–8	0.5	1
	IR	0.5–8	1	8
	HR	0.5–8	1	8

[a] S, viridans group streptococci ($n = 42$) susceptible to penicillin (MIC, ≤0.01 to 0.12 μg/ml); IR, viridans group streptococci ($n = 8$) intermediately resistant to penicillin (MIC, 0.25 to 2 μg/ml); HR, viridans group streptococci ($n = 16$) highly resistant to penicillin (MIC, ≥4 μg/ml).
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

The 11 strains highly resistant to erythromycin (MIC, >128 μg/ml) had cross-resistance to the other 14- and 15-membered macrolides (MIC, >128 μg/ml), whereas the MICs of the 16-membered compounds tested ranged from 8 to >128 μg/ml. The 12 erythromycin-resistant strains (MICs, 1 to 4 μg/ml) were also resistant to clarithromycin, roxithromycin, dirithromycin, and azithromycin (MICs, 1 to 8 μg/ml). Josamycin and spiramycin inhibited 10 of these 12 erythromycin-resistant strains at MICs of ≤0.25 μg/ml. The MICs of diacetyl-midecamycin for these 12 strains ranged from 0.5 to 2 μg/ml.

All erythromycin-susceptible and intermediately resistant strains were inhibited at 2 μg or less of the streptogramin quinupristin-dalfopristin per ml. The MICs of quinupristin-dalfopristin for the strains highly resistant to erythromycin ranged from 0.5 to 2 μg/ml for three strains, and the MIC for the remaining eight strains was 8 μg/ml.

S. mitis was the species most frequently isolated (83.3% of all strains) and showed the highest rates of penicillin (40%) and erythromycin (43.6%) resistance.

DISCUSSION

This study showed high rates of penicillin and erythromycin resistance among viridans group streptococci isolated from

TABLE 2. In vitro activities of eight macrolide antibiotics and quinupristin-dalfopristin against viridans group streptococci isolated from blood samples of neutropenic cancer patients

Antibiotic	Type of viridans group streptococcus[a]	MIC (μg/ml)[b]		
		Range	50%	90%
Erythromycin	S	≤0.01–0.12	≤0.01	0.06
	R	1–>128	4	>128
Clarithromycin	S	≤0.01–0.06	≤0.01	0.03
	R	0.25	2	>128
Roxithromycin	S	≤0.01–0.12	≤0.01	0.06
	R	0.5–>128	4	>128
Dirithromycin	S	0.03–0.5	0.06	0.25
	R	1–>128	8	>128
Azithromycin	S	≤0.01–0.25	0.03	0.06
	R	0.5–>128	4	>128
Josamycin	S	0.03–0.12	0.12	0.12
	R	0.06–>128	1	>128
Diacetyl-midecamycin	S	0.06–0.5	0.25	0.25
	R	0.25–>32	2	>32
Spiramycin	S	≤0.01–0.12	0.06	0.12
	R	0.03–>128	0.5	>128
Quinupristin-dalfopristin	S	0.25–1	0.5	1
	R	0.5–8	1	8

[a] S, viridans group streptococci (n = 40) susceptible to erythromycin (MIC, ≤0.01 to 0.25 μg/ml); R, viridans group streptococci (n = 23) highly resistant to erythromycin (MIC, ≥1 μg/ml). Only three strains were intermediately resistant to erythromycin (MIC, 0.5 μg/ml).

[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

blood samples of neutropenic cancer patients. The percentages of erythromycin resistance were significantly higher for penicillin-resistant strains than those for penicillin-susceptible strains. As previously reported (1a, 6), *S. mitis* was the species most frequently isolated and was less susceptible to penicillin than other viridans group streptococci. Furthermore, we also observed the highest rate of erythromycin resistance in this species. These findings argue against the clinical usefulness of erythromycin to prevent viridans group streptococcal bacteremia. In fact, the addition of erythromycin to ciprofloxacin as a prophylactic agent was found to be ineffective in a previous report (33).

The development of new macrolides that improve the chemical, biological, and pharmacokinetic properties of erythromycin has renewed the interest in this new macrolide group for the prevention of viridans group streptococcal bacteremia. In two previously published studies, the addition of roxithromycin to a fluoroquinolone was shown to be an effective approach to the prevention of streptococcal bacteremia in neutropenic patients (16, 23). However, our study showed that the in vitro activities of all macrolide antibiotics tested against the penicillin-resistant viridans group streptococci were lower than against the penicillin-susceptible group. Furthermore, we found that all isolates of viridans group streptococci that were resistant to erythromycin showed cross-resistance to the 14- and 15-membered macrolides. In particular, roxithromycin showed in vitro activity similar to that of erythromycin. Although clarithromycin was the most active agent among the macrolides tested, it had MICs that were only 1 dilution lower than those of erythromycin.

Generally, the 16-membered macrolides were less active in vitro than erythromycin, but they were slightly more active than erythromycin against erythromycin-resistant strains. In previous reports, the new semisynthetic injectable streptogramin quinupristin-dalfopristin demonstrated good in vitro activities against most gram-positive bacteria (3, 15, 26, 28, 30). In our study, quinupristin-dalfopristin showed good in vitro activities against erythromycin-susceptible and intermediately resistant strains (MICs, ≤2 μg/ml), but the MIC for eight strains highly resistant to erythromycin was 8 μg/ml. The clinical impact of these in vitro data is not clear, because there is a lack of clinical trials using this drug for neutropenic cancer patients and the breakpoint of resistance of this streptogramin has not been well defined.

In summary, this study shows that resistance to penicillin and erythromycin among viridans group streptococci isolated from blood samples of neutropenic cancer patients is frequent. In vitro activities of all macrolide antibiotics tested were higher against penicillin-susceptible strains than against penicillin-resistant strains. The new 14- and 15-membered macrolides tested had activities similar to that of erythromycin, and all erythromycin-resistant isolates were also resistant to these new compounds. These data make macrolides unsuitable prophylactic agents against viridans streptococcal bacteremia in neutropenic cancer patients. Therefore, the prophylaxis of streptococcal bacteremia for this patient population should be reevaluated and clinical studies with other antimicrobial agents, such as quinupristin-dalfopristin, are needed.

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