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Comparative In Vitro Activities of Linezolid, Quinupristin-Dalfopristin, Moxifloxacin, and Trovafloxacin against Erythromycin-Susceptible and -Resistant Streptococci

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The in vitro activities of the new agents linezolid, quinupristin-dalfopristin, moxifloxacin, and trovafloxacin were determined and compared with those of penicillin, clindamycin, and four macrolides against 53 erythromycin-resistant *Streptococcus pneumoniae*, 117 *S. pyogenes* (64 erythromycin-susceptible and 53 -resistant), and 101 *S. agalactiae* (53 erythromycin-susceptible and 48 -resistant) isolates. Differentiation of macrolide resistance phenotypes was performed by the double-disk method. The genetic basis for macrolide resistance in 52 strains was also determined. The M phenotype was found in 84.9, 6.3, and 1.9% of *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae* isolates, respectively. These strains were susceptible to miocamycin and clindamycin. Strains with the inducible phenotype accounted for 27.1% of *S. agalactiae* isolates and 9.4% each of *S. pyogenes* and *S. pneumoniae* isolates. All erythromycin-resistant isolates were also resistant to the 14- and 15-membered macrolides tested. Strains with all three phenotypes were susceptible to ≤2 μg of linezolid per ml. Quinupristin-dalfopristin exhibited good in vitro activity against all strains, irrespective of their resistance to erythromycin (MICs at which 90% of the isolates tested were inhibited [MIC_{90}s], 0.2 to 1 μg/ml). Against the erythromycin-resistant *S. pyogenes* and *S. agalactiae* strains, moxifloxacin and trovafloxacin were the most active agents (MIC_{90}s, 0.1 μg/ml). The new antimicrobials evaluated may be alternative agents to treat infections caused by macrolide-resistant as well as macrolide-susceptible streptococci.

Erythromycin has been considered to be the principal alternative agent for the treatment of gram-positive streptococcal infections in penicillin-allergic patients. However, increased incidence of erythromycin resistance in *Streptococcus pyogenes* has been reported in several parts of the world (6, 7, 19, 21, 25). In our area, erythromycin resistance in *S. pyogenes* increased from 2.6% in 1995 to 17.1% in 1996 (4). The prevalence of infections caused by penicillin-resistant and multidrug-resistant pneumococci has been increasing over the last 2 decades (2, 9, 10). Erythromycin resistance is also increasing in *Streptococcus agalactiae* in some countries (29; M. K. H. McGavin, A. McGeer, J. C. de Azavedo, L. Trpeski, S. Pong-Porter, C. Duncan, and D. E. Low, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1224, p. 159, 1999). The current rates of erythromycin resistance in our area are about 40% for *Streptococcus pneumoniae*, 26% for *S. pyogenes*, and 15% for *S. agalactiae*.

Two mechanisms of macrolide resistance in streptococci have been described: (i) target site modification mediated by erythromycin resistance methylases encoded by *erm* genes, whose phenotypic expression can be inducible or constitutive, and (ii) an efflux mechanism encoded by *mef* genes (*mefA* or *mefE*). Because macrolide resistance in streptococci appears to have increased worldwide over the past decade, new therapeutic alternatives are needed.

Compared with older quinolones, moxifloxacin and trovafloxacin have enhanced activity against gram-positive organisms and anaerobes and maintain the activity of older quinolones against gram-negative organisms. However, because of hepatotoxicity, the European Union has banned trovafloxacin. Quinupristin-dalfopristin is a new streptogramin antibiotic with activity against gram-positive aerobes. Previous studies have shown that this compound is highly active against streptococci, including multidrug-resistant strains (3, 14). Linezolid belongs to a new class of synthetic agents, the oxazolidinones, and has activity against multidrug-resistant gram-positive bacteria, including methicillin-resistant staphylococci, penicillin-resistant pneumococci, and vancomycin-resistant enterococci (27, 30).

The purpose of this study was to determine the in vitro activities of the new antimicrobials linezolid, quinupristin-dalfopristin, moxifloxacin, and trovafloxacin against erythromycin-resistant streptococci and to compare these activities with those of six other antibiotics. The mechanisms of macrolide resistance were also examined.

(This study was presented in part at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 26 to 29 September 1999.)

MATERIALS AND METHODS

A total of 271 streptococcal isolates were tested. These included 53 erythromycin-resistant *S. pneumoniae*, 117 *S. pyogenes* (64 erythromycin-susceptible and 53 -resistant), and 101 *S. agalactiae* (53 erythromycin-susceptible and 48 -resistant) isolates. Only one isolate per patient was studied to avoid duplication. Organisms were identified by standard methods, including agglutination with latex (Slidex pneumo-kit, Slidex Strepto A, and Slidex Strepto B; bioMérieux, Marcy L'Etoile, France).

Susceptibility testing was performed by the agar dilution method according to the guidelines of the National Committee for Clinical Laboratory Standards (15, 16). Mueller-Hinton agar supplemented with 5% sheep blood was used. Approximately 10^4 CFU was inoculated per spot with a Steers replicator. In each test, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 were used as internal controls. Plates were incubated overnight at 35°C in air. The MIC was defined as the lowest concentration of each antimicrobial which completely inhibited bacterial growth.

The following antimicrobial agents were used and obtained from the indicated

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TABLE 1. In vitro activities of 10 antimicrobial agents against 271 streptococcal strains

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		Range	MIC_{50}	MIC_{90}
Erythromycin-resistant *S. pneumoniae* (53)	Penicillin	0.03–4	1	2
	Erythromycin	1–>64	64	>64
	Roxithromycin	0.5–>64	64	>64
	Azithromycin	1–>64	64	>64
	Miocamycin	0.1–64	2	32
	Clindamycin	0.03–>64	64	>64
	Quinupristin-dalfopristin	0.2–1	0.5	1
	Linezolid	1–2	2	2
	Moxifloxacin	0.06–1	0.1	1
	Trovafloxacin	0.03–2	0.06	0.1
Erythromycin-susceptible *S. pyogenes* (64)	Penicillin	0.008–0.03	0.008	0.01
	Erythromycin	0.01–0.03	0.03	0.03
	Roxithromycin	0.06–0.2	0.06	0.1
	Azithromycin	0.03–0.3	0.06	0.06
	Miocamycin	0.1–0.5	0.1	0.2
	Clindamycin	0.03–0.06	0.03	0.06
	Quinupristin-dalfopristin	0.1–0.2	0.2	0.2
	Linezolid	1–2	2	2
	Moxifloxacin	0.03–0.1	0.06	0.1
	Trovafloxacin	0.03–0.1	0.06	0.1
Erythromycin-resistant *S. pyogenes* (53)	Penicillin	0.004–0.03	0.008	0.01
	Erythromycin	1–>64	8	16
	Roxithromycin	1–>64	16	32
	Azithromycin	2–>64	8	16
	Miocamycin	0.1–>64	0.1	0.2
	Clindamycin	0.01–>64	0.03	0.06
	Quinupristin-dalfopristin	0.1–0.5	0.2	0.2
	Linezolid	1–2	2	2
	Moxifloxacin	0.03–0.2	0.1	0.1
	Trovafloxacin	0.03–0.5	0.06	0.1
Erythromycin-susceptible *S. agalactiae* (53)	Penicillin	0.01–0.06	0.03	0.06
	Erythromycin	0.01–0.03	0.03	0.03
	Roxithromycin	0.06–0.1	0.1	0.1
	Azithromycin	0.03–0.3	0.03	0.03
	Miocamycin	0.2	0.2	0.2
	Clindamycin	0.03–0.06	0.03	0.06
	Quinupristin-dalfopristin	0.5–1	0.5	0.5
	Linezolid	2	2	2
	Moxifloxacin	0.06–0.1	0.06	0.1
	Trovafloxacin	0.06–0.1	0.1	0.1
Erythromycin-resistant *S. agalactiae* (48)	Penicillin	0.03–0.06	0.03	0.06
	Erythromycin	1–>64	8	>64
	Roxithromycin	2–>64	16	>64
	Azithromycin	1–>64	16	>64
	Miocamycin	0.2–>64	8	64
	Clindamycin	0.03–>64	4	>64
	Quinupristin-dalfopristin	0.5	0.5	0.5
	Linezolid	1–2	2	2
	Moxifloxacin	0.03–0.1	0.06	0.1
	Trovafloxacin	0.06–0.1	0.06	0.1

manufacturers: penicillin, Compañía Española de la Penicilina y Antibióticos, S.L., Madrid, Spain; erythromycin, Abbott, Madrid, Spain; roxithromycin, Hoechst Marion Roussel, S.A., Madrid, Spain; azithromycin, Farmasierra, S.A., Madrid, Spain; miocamycin, Menarini, S.A., Barcelona, Spain; clindamycin and linezolid, Pharmacia & Upjohn, Barcelona, Spain; quinupristin-dalfopristin, Rhône-Poulenc Rorer, Madrid, Spain; moxifloxacin, Bayer, Barcelona, Spain; and trovafloxacin, Pfizer, New York, N.Y.

Erythromycin resistance phenotypes were determined by the double-disk test (20) with erythromycin (15 μg) and clindamycin (2 μg) disks on Mueller-Hinton agar supplemented with 5% sheep blood. Plates were incubated overnight at 35°C in air. The presence of the erythromycin resistance genes in 52 (13 *S. pneumoniae*, 25 *S. pyogenes*, and 14 *S. agalactiae*) randomly selected isolates was investigated by PCR (22, 24). Primer sets specific for the *ermA*, *ermB*, *ermC*, and *ermTR* genes were used for the identification of erythromycin resistance genes. The presence of the *ermTR* gene was confirmed by *Hin*fI digestion. PCR with *mefA* and *mefE* primers was performed to confirm the presence of the efflux system.

RESULTS AND DISCUSSION

Results of MIC determinations are listed in Table 1. Inter-

TABLE 2. Distribution of erythromycin resistance genes among macrolide-resistant streptococci (13 *S. pneumoniae*, 25 *S. pyogenes*, and 14 *S. agalactiae* isolates) of different phenotypes

Organism	Resistance phenotype	No. of strains tested	No. of strains with the following gene(s):				
			mefA or *mefE*	*ermA*	*ermB*	*ermC*	*ermTR*
S. pneumoniae	M	1	1				
	iMLS	1			1		1
	cMLS	11			11		
S. pyogenes	M	22	22				
	iMLS	3			1		3
	cMLS						
S. agalactiae	M	1	1				
	iMLS	7			3		5
	cMLS	6			4		2

mediate susceptibility and resistance to penicillin were found in 52.8 and 37.8%, respectively, of *S. pneumoniae* isolates. Both *S. pyogenes* and *S. agalactiae*, including those strains which were erythromycin resistant, were uniformly susceptible to pencillin. Of the 14- and 15-membered macrolides, erythromycin showed slightly better activity than roxithromycin and azithromycin against erythromycin-susceptible streptococci. All erythromycin-resistant isolates were also resistant to the 14- and 15-membered lactone ring agents tested, roxithromycin and azithromycin, respectively. Miocamycin, the 16-membered macrolide tested, had the greatest activity against erythromycin-resistant strains, retaining full activity against M-phenotype isolates of *S. pyogenes*, *S. pneumoniae*, and *S. agalactiae*. The widespread use of macrolides might contribute to the high incidence of erythromycin resistance among streptococci (mainly *S. pneumoniae* and *S. pyogenes*) observed in many countries (6, 19, 21, 29). Thus, new agents are needed as alternatives to penicillin for the prophylaxis or treatment of infections caused by streptococci in penicillin-allergic patients, as well as those caused by penicillin-resistant pneumococci.

Quinupristin-dalfopristin exhibited good in vitro activities against all strains tested, irrespective of their resistance to erythromycin. Although against macrolide-susceptible isolates quinupristin-dalfopristin had 8- to 16-fold less activity than erythromycin, *S. pyogenes*, and *S. agalactiae* were highly susceptible to this new streptogramin, with MICs at which 90% of the tested isolates were inhibited (MIC_{90}s) ranging from 0.2 to 0.5 μg/ml. The MIC_{50} and MIC_{90} of this antibiotic for *S. pneumoniae* were similar to those described by other authors (3, 14). Among *S. pyogenes* and *S. agalactiae* we found quinupristin-dalfopristin MIC_{90}s that were slightly lower than those reported by Barry et al. (3).

Linezolid was active against all streptococci tested at ≤2 μg/ml. For *S. pyogenes*, as well as *S. pneumoniae* and *S. agalactiae*, the linezolid MIC_{90} was 2 μg/ml. The results of this study agree with those of previous reports (27, 30) on in vitro susceptibility to linezolid. This suggests that linezolid may be a therapeutic option for the treatment of infections due to erythromycin-resistant or penicillin-resistant streptococci.

The new fluoroquinolones included in this study, moxifloxacin and trovafloxacin, showed high activities against both the erythromycin-resistant and erythromycin-susceptible streptococcal strains tested. Moxifloxacin showed excellent in vitro activity against all strains, with MIC_{90}s of 1 μg/ml for *S. pneumoniae* and 0.1 μg/ml for both *S. pyogenes* and *S. agalactiae*. Like Woodcock et al. (28), we found that against *S. pyogenes* and *S. agalactiae* the activities of moxifloxacin were comparable to those of trovafloxacin. Among macrolide-resistant pneumococci, both fluoroquinolones showed potent activity, as several authors have already reported (9, 26), with the trovafloxacin MIC_{50}s and MIC_{90}s being slightly lower than those of moxifloxacin. Nevertheless, an increasing prevalence of pneumococci with reduced susceptibility to fluoroquinolones (5, 13), as well as the isolation of penicillin-resistant *S. pneumoniae* strains that were highly resistant to trovafloxacin (9), has recently been reported. Therefore, caution in the use of these antibiotics must be exercised and surveillance is necessary in order to detect the emergence of or increase in resistance to these new fluoroquinolones.

The so-called M phenotype was found in 84.9, 6.3, and 1.9% of *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae* isolates, respectively. These strains were susceptible to clindamycin and miocamycin and resistant at a low level to erythromycin. The constitutive macrolide-lincosamide-streptogramin B (cMLS) phenotype was observed for *S. pneumoniae* (88.7%), *S. agalactiae* (66.6%), and *S. pyogenes* (5.7%) strains which showed high-level resistance to erythromycin, clindamycin, and miocamycin. Strains with the inducible MLS (iMLS) phenotype accounted for 27.1% of *S. agalactiae* isolates and 9.4% each of *S. pyogenes* and *S. pneumoniae* isolates.

Resistance to macrolides in our *S. pneumoniae* isolates is mainly due to the constitutive MLS phenotype, as recently described by Baquero et al. (2) in Spain and Oster et al. (18) in Italy. By contrast, the M phenotype predominates in pneumococcal strains isolated in Japan (17), Canada (11), and the United States (23). The erythromycin-resistant *S. pyogenes* isolates from our study were predominantly (84.9%) of the M phenotype, whereas the erythromycin-resistant *S. agalactiae* isolates accounted only for 1.9% of the isolates with this phenotype. The incidence of the M phenotype of erythromycin resistance among isolates of *S. pyogenes* in this study is similar to that reported by other groups in Spain (1, 19) but different from that (around 50%) reported in Italian surveys (8) and in Greece (25). The 16-membered macrolides and clindamycin might be considered alternative agents for the treatment of infections caused by strains showing this phenotype of macrolide resistance.

The genotypes of the 13 *S. pneumoniae*, 25 *S. pyogenes*, and 14 *S. agalactiae* isolates are summarized in Table 2. All the *S. pneumoniae* isolates with a cMLS phenotype were positive for the *ermB* gene. No *ermTR* gene was detected in pneumococcal strains with a cMLS phenotype. Of the six cMLS-phenotype *S.*

agalactiae isolates, two were positive with primers specific for the *ermTR* gene and the remaining isolates were positive with primers for the *ermB* gene. Three isolates (1 *S. pneumoniae*, 1 *S. pyogenes*, and 1 *S. agalactiae* isolate) bearing the iMLS phenotype possessed both the *ermTR* and *ermB* genes.

Among *S. pyogenes* isolates, we found the *mefA* gene in all isolates with the M phenotype and the *ermTR* gene in the three isolates tested with the iMLS phenotype. This corresponds with recent reports by Kataja et al. (12) and de Azavedo et al. (7). We did not find the *mefA* gene in the iMLS *S. pyogenes* isolates tested, whereas Giovanetti et al. (8) detected this gene in 30 of 60 iMLS isolates tested. However, we found one *S. pyogenes* isolate bearing the iMLS phenotype which possessed both the *ermB* and *ermTR* genes. The MIC of erythromycin for these isolate (8 μg/ml) was higher than those for the remaining two iMLS isolates (1 μg/ml each) harboring only the *ermTR* gene.

This study shows that the 14- and 15-membered macrolides had poor activities against clinical isolates of erythromycin-resistant streptococci. The 16-membered macrolide tested, miocamycin, as well as clindamycin, showed good activity against streptococci with the M erythromycin resistance phenotype. In areas where streptococcal resistance to erythromycin is common, determination of erythromycin resistance phenotypes can be helpful in the selection of an appropriate alternative therapy for penicillin-allergic patients.

The new agents tested, linezolid, quinupristin-dalfopristin, moxifloxacin, and trovafloxacin, showed excellent activities against the *S. pneumoniae*, *S. pyogenes*, and *S. agalactiae* isolates studied, irrespective of their susceptibility to erythromycin. On the basis of these results, we suggest that any of the new antimicrobials evaluated might offer a good therapeutic option in infections caused by macrolide-susceptible as well as macrolide-resistant streptococcal isolates. Further evaluations of these agents are warranted.

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