ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2006, p. 4191–4194 Vol. 50, No. 12
0066-4804/06/$08.00+0 doi:10.1128/AAC.01110-06

Activity of DX-619 Compared to Other Agents against Viridans Group Streptococci, *Streptococcus bovis*, and *Cardiobacterium hominis*▽

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Received 1 September 2006/Returned for modification 19 September 2006/Accepted 19 September 2006

Against 198 viridans group streptococci, 25 *Streptococcus bovis* strains, and 5 *Cardiobacterium hominis* strains, MICs of DX-619, a des-F(6)-quinolone, were between 0.004 and 0.25 μg/ml. These MICs were lower than those of other quinolones (≤0.008 to >32 μg/ml). β-Lactam MICs were between ≤0.008 and 16 μg/ml. Azithromycin resistance was found in most species, while most were telithromycin susceptible. Glycopeptides and linezolid were active against viridans group strains but inactive against *C. hominis*.

Organisms in the viridans streptococcal group are normal inhabitants of the human respiratory tract above the larynx. The classification of these organisms has been a matter of dispute and is still in a state of flux, with disagreements in the precise nomenclature and the need for laborious and time-consuming methods for accurate and reproducible species identification (14, 16). Such methods are beyond the capability of the routine clinical microbiology laboratory, so these strains usually remain unidentified to the species level.

With proper classification, it has become clear that disease caused by viridans group streptococci is, to a large extent, species specific. *Streptococcus mutans* strains are involved in the pathogenesis of dental caries, and those in the group comprising *S. mitis*, *S. salivarius*, and *S. sanguinis* are the main causative organisms in subacute bacterial endocarditis (7). By contrast, organisms grouped together by the United Kingdom classification as *S. milleri* (*S. anginosus*, *S. constellatus*, *S. intermedius*; beta-hemolytic group F streptococci) are involved (alone or in combination with other aerobic, microaerophilic, and anaerobic species) in the pathogenesis of deep pyogenic processes, such as liver and brain abscesses (13). *Cardiobacterium hominis*, a gram-negative rod, is another cause of subacute endocarditis and was included because of the lack of susceptibility data for this species (6, 11). Although *S. bovis* is not classified as a viridans group streptococcus, it was included in this study because of the paucity of data related to quinolone resistance in this species.

It is possible that the pneumococcus originally obtained its resistance transposon(s) from the viridans group more than 30 years ago; Janoir et al. (8) have reported in vitro exchange of fluoroquinolone resistance determinants between *Streptococcus pneumoniae* and viridans group streptococci in vitro. Additionally, resistance to β-lactams and other agents is increasingly seen for viridans group streptococci, necessitating a search for other therapeutic modalities (4, 13, 15). DX-619 is a new des-F(6)-quinolone with excellent activity against gram-positive organisms (1, 5, 17). In this study we tested the activity of DX-619 and compared it to the activities of sitafloxacin, levofloxacin, moxifloxacin, gatifloxacin, penicillin G, amoxicillin/clavulanate, azithromycin, telithromycin, vancomycin, teicoplanin, and linezolid against a spectrum of viridans group streptococci, *S. bovis* strains, and *C. hominis* strains.

Viridans group streptococci (Table 1) were all recent clinical isolates identified to the species level by standard CDC-recommended methodology (6, 14). Apart from 14 strains isolated between 1997 and 1999, all others were isolated from sites in North America, Latin America, and Europe between 2001 and 2004. A total of 198 viridans group streptococci, 25 *S. bovis* strains, and 5 *C. hominis* strains were tested. Viridans group streptococci were cultured from blood, wound drainage, sputum, abscesses, pleural fluid, invasive pulmonary infections, sinuses, eye, bronchoalveolar lavage specimens, cerebrospinal fluid, tissue, and ear/nose/throat. All *C. hominis* strains were obtained from the American Type Culture Collection (Rockville, Md.). Strains were frozen at −70°C in double-strength skim milk (Difco Laboratories, Detroit, Mich.) before use. DX-619 and sitafloxacin powders were obtained from Daiichi Pharmaceutical Co., Ltd., penicillin G from Sigma, Inc., St. Louis, Mo., and the remaining compounds from their respective manufacturers.

Susceptibility testing was done to determine agar dilution MIC by use of Mueller-Hinton plates supplemented with 5% sheep blood (3). Inocula were 10^4 CFU/spot, and plates were incubated overnight at 35°C in ambient air. *C. hominis* strains, which require increased humidity for growth (11), were incubated in sealed jars with moist paper towels at the bottom of the jar. Standard quality control strains recommended by CLSI (*Staphylococcus aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619) were included in each run (3).

Quinolone-resistant strains were tested for mutations in portions of the *gyrA* and *parC* genes by PCR and sequencing by use of the following primers: gA2 (5′-TYATYGAYTAYGCYATGAGTG-3′) and gA1 (5′-GCRCYATCHCCRTCCATDGAACC-3′) for *gyrA* amplification and pC1 (5′-GTCCCTKGAGGAYATYATGGGAG-3′) and pC2 (5′-ARRCGNGCYTCNGTATAACGC-3′) for *parC* amplification (Y. Onodera, personal

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▽ Published ahead of print on 16 October 2006.

TABLE 1. Comparative MICs (μg/ml) against strains tested

Species (no. of strains) and drug	MIC range	MIC_{50}	MIC_{90}
S. mitis (25)			
DX-619	0.004–0.03	0.016	0.03
Sitafloxacin	0.03–0.25	0.06	0.12
Levofloxacin	1–2	2	2
Moxifloxacin	0.12–0.25	0.12	0.25
Gatifloxacin	0.25–1	0.5	0.5
Penicillin G	≤0.008–8	0.12	2
Amoxicillin-clavulanate	0.03–16	0.06	1
Azithromycin	0.03–>64	2	>64
Telithromycin	0.008–0.25	0.03	0.12
Vancomycin	0.25–0.5	0.5	0.5
Teicoplanin	0.06–0.5	0.12	0.25
Linezolid	1–2	1	2
S. salivarius (25)			
DX-619	0.004–0.03	0.016	0.03
Sitafloxacin	0.03–0.25	0.06	0.06
Levofloxacin	1–4	1	2
Moxifloxacin	0.12–0.5	0.25	0.5
Gatifloxacin	0.12–1	0.25	1
Penicillin G	0.03–1	0.12	0.5
Amoxicillin-clavulanate	0.03–1	0.12	0.5
Azithromycin	0.03–>64	0.06	>64
Telithromycin	0.008–0.25	0.03	0.12
Vancomycin	0.25–1	0.5	1
Teicoplanin	0.12–0.5	0.25	0.25
Linezolid	1–4	1	2
S. sanguinis (24)			
DX-619	0.004–0.03	0.016	0.03
Sitafloxacin	0.03–0.25	0.06	0.25
Levofloxacin	0.5–2	1	2
Moxifloxacin	0.12–0.5	0.25	0.25
Gatifloxacin	0.12–1	0.5	0.5
Penicillin G	0.016–4	0.12	1
Amoxicillin-clavulanate	0.03–8	0.25	2
Azithromycin	0.03–>64	0.12	>64
Telithromycin	0.004–1	0.03	0.25
Vancomycin	0.25–1	0.5	1
Teicoplanin	0.06–0.25	0.12	0.25
Linezolid	0.5–2	1	2
S. mutans (24)			
DX-619	0.004–0.03	0.016	0.03
Sitafloxacin	0.016–0.12	0.03	0.06
Levofloxacin	0.25–2	1	2
Moxifloxacin	0.06–0.25	0.12	0.25
Gatifloxacin	0.06–0.5	0.25	0.5
Penicillin G	≤0.008–2	≤0.008	0.06
Amoxicillin-clavulanate	≤0.016–4	≤0.016	0.06
Azithromycin	≤0.016–>64	0.06	0.12
Telithromycin	≤0.004–0.25	0.03	0.25
Vancomycin	0.5–1	0.5	1
Teicoplanin	0.06–1	0.25	0.25
Linezolid	0.25–4	1	2
S. anginosus (25)			
DX-619	0.004–0.016	0.016	0.016
Sitafloxacin	0.016–0.25	0.06	0.12
Levofloxacin	0.5–2	1	2
Moxifloxacin	0.06–0.25	0.12	0.25
Gatifloxacin	0.06–0.5	0.25	0.5
Penicillin G	≤0.008–0.25	0.06	0.06
Amoxicillin-clavulanate	≤0.016–0.25	0.12	0.12
Azithromycin	0.03–>64	0.12	>64
Telithromycin	≤0.004–0.25	0.03	0.12
Vancomycin	0.25–1	0.5	1
Teicoplanin	0.06–0.5	0.12	0.25
Linezolid	1–4	2	4
S. constellatus (23)			
DX-619	0.004–0.016	0.008	0.016
Sitafloxacin	0.016–0.06	0.03	0.06
Levofloxacin	0.25–2	0.5	1
Moxifloxacin	0.06–0.25	0.12	0.25
Gatifloxacin	0.06–0.5	0.25	0.25
Penicillin G	0.016–0.06	0.06	0.06
Amoxicillin-clavulanate	≤0.016–0.25	0.12	0.25
Azithromycin	0.03–0.12	0.06	0.12
Telithromycin	0.008–0.06	0.03	0.03
Vancomycin	0.5–1	1	1
Teicoplanin	0.06–0.25	0.06	0.12
Linezolid	0.5–4	1	2
S. intermedius (27)			
DX-619	0.004–0.016	0.016	0.016
Sitafloxacin	0.03–0.12	0.03	0.06
Levofloxacin	0.5–1	1	1
Moxifloxacin	0.06–0.25	0.12	0.25
Gatifloxacin	0.06–0.5	0.25	0.5
Penicillin G	0.03–0.5	0.06	0.06
Amoxicillin-clavulanate	0.03–0.25	0.12	0.25
Azithromycin	0.03–>64	0.12	0.25
Telithromycin	0.016–0.06	0.03	0.06
Vancomycin	0.25–1	0.5	1
Teicoplanin	0.06–0.5	0.12	0.25
Linezolid	1–4	2	2
S. oralis (25)			
DX-619	0.008–0.06	0.016	
Sitafloxacin	0.06–0.5	0.12	0.03
Levofloxacin	1–16	2	0.25
Moxifloxacin	0.12–4	0.25	2
Gatifloxacin	0.25–8	0.5	0.5
Penicillin G	0.016–4	0.06	1
Amoxicillin-clavulanate	0.03–8	0.06	2
Azithromycin	0.03–16	0.5	4
Telithromycin	0.016–1	0.03	4
Vancomycin	0.25–0.5	0.5	0.12
Teicoplanin	0.06–0.25	0.12	0.5
Linezolid	1–>8	2	0.25
S. bovis (25)			
DX-619	0.008–0.25	0.016	0.12
Sitafloxacin	0.06–2	0.12	0.5
Levofloxacin	1–>32	2	>32
Moxifloxacin	0.12–16	0.5	4
Gatifloxacin	0.5–>32	1	8
Penicillin G	0.016–0.12	0.06	0.06
Amoxicillin-clavulanate	0.06–0.25	0.06	0.12
Azithromycin	0.06–>64	0.12	>64
Telithromycin	0.008–>8	0.03	0.5
Vancomycin	0.25–0.5	0.25	0.5
Teicoplanin	0.12–0.5	0.5	0.5
Linezolid	1–4	2	4
C. hominis (5)			
DX-619	0.016–0.03	0.016	
Sitafloxacin	≤0.008–0.06	≤0.008	
Levofloxacin	≤0.06–0.25	≤0.06	
Moxifloxacin	0.03–0.12	0.03	
Gatifloxacin	≤0.016–0.25	≤0.016	
Penicillin G	≤0.008–2	≤0.008	
Amoxicillin-clavulanate	≤0.016–0.5	≤0.016	
Azithromycin	0.5–1	0.5	
Telithromycin	0.25–1	1	
Vancomycin	2–>4	>4	
Teicoplanin	2–>4	>4	
Linezolid	8–>8	>8	

TABLE 2. Quinolone susceptibilities and resistance mechanisms in 10 isolates displaying levofloxacin MICs of ≥4 μg/ml

Strain no., species	MIC (μg/ml) against the following quinolone:					Mutation(s) in QRDR[a]		Efflux mechanism (no. of doubling dilutions)[b]
	DX-619	Levofloxacin	Moxifloxacin	Sitafloxacin	Gatifloxacin	GyrA	ParC	
68, *S. salivarius*	0.03	4	0.5	0.25	1	NC	S79R, M116I	+ (2)
116, *S. bovis*	0.06	>32	4	0.5	8	H43D, G79C	S79F, D83N	−
118, *S. bovis*	0.016	4	0.5	0.12	0.5	NC	M116I	+ (1)
121, *S. bovis*	0.12	4	2	0.25	2	S81L	NC	−
122, *S. bovis*	0.12	8	2	0.25	2	S81L	NC	−
124, *S. bovis*	0.12	>32	8	1	16	S81F	Y15D, S79F	−
125, *S. bovis*	0.03	4	0.5	0.12	1	NC	Y15D	−
132, *S. bovis*	0.25	>32	16	2	>32	S81L	S79Y	−
193, *S. oralis*	0.06	16	4	0.5	8	NC	S79Y	+ (1)
216, *S. oralis*	0.03	8	2	0.25	2	S81F, Y107I	D83N	+ (1)

[a] NC, no change compared to susceptible strain or susceptible *S. pneumoniae* R6. Used is *S. pneumoniae* R6 numbering (sequence NCBI accession numbers AAK99902 [GyrA] and AAK99561 [ParC]).
[b] −, efflux mechanism absent; +, efflux mechanism present.

communication). Fragments of deduced amino acid sequences of GyrA (amino acid positions 20 to 110, *S. pneumoniae* R6 numbering, NCBI accession number AAK99902) and ParC (amino acid positions 8 to 120, *S. pneumoniae* R6 numbering, NCBI accession number AAK99561) were compared to sequences from a susceptible strain of the same species and the *S. pneumoniae* R6 susceptible strain.

All resistant strains were tested for the presence of a quinolone efflux mechanism by comparing ciprofloxacin agar dilution MICs in the presence and absence of 10 μg/ml of reserpine (a known efflux pump inhibitor). A decrease of MIC of at least fourfold was used to define the presence of an efflux mechanism, although an efflux mechanism was believed to be present when the MIC (in the presence of reserpine) was at least twofold less (1 doubling dilution) than the MIC in the absence of reserpine (tests were done in duplicate) (2).

MICs (μg/ml) for the two quality control strains were as follows. For *S. aureus* ATCC 29213, the MICs of DX-619 were 0.004 (once) and 0.008 (eight times); that of sitafloxacin was 0.03 (nine times); that of levofloxacin, 0.25 (nine times); that of moxifloxacin, 0.06 (nine times); those of gatifloxacin, 0.06 (twice) and 0.12 (seven times); those of penicillin G, 0.5 (three times), 1 (four times), and 2 (twice); those of amoxicillin/clavulanate, 0.25 (twice) and 0.5 (seven times); those of azithromycin, 0.5 (once) and 1 (eight times); that of telithromycin, 0.12 (nine times); those of vancomycin, 0.5 (four times) and 1 (five times); that of teicoplanin, 1 (nine times); and those of linezolid, 2 (four times) and 4 (five times). For *S. pneumoniae* ATCC 49619, the MIC of DX-619 was 0.016 (nine times); that of sitafloxacin, 0.06 (nine times); those of levofloxacin were 1 (seven times) and 2 (twice); those of moxifloxacin, 0.12 (three times) and 0.25 (six times); those of gatifloxacin, 0.25 (three times) and 0.5 (six times); those of penicillin G, 0.25 (once) and 0.5 (eight times); those of amoxicillin/clavulanate, 0.06 (eight times) and 0.12 (once); those of azithromycin, 0.12 (six times) and 0.25 (three times); that of telithromycin, 0.03 (nine times); those of vancomycin, 0.25 (eight times) and 0.5 (once); that of teicoplanin, 0.12 (nine times); and those of linezolid, 1 (four times) and 2 (five times).

Results of MIC testing are presented in Table 1. As can be seen, DX-619 MICs for all strains ranged between 0.004 and 0.25 μg/ml, with an overall MIC_{50} of 0.016 μg/ml and MIC_{90} of 0.03 μg/ml. By comparison, MICs of other quinolones ranged between ≤0.008 and >32 μg/ml. However, when results for *S. bovis* were excluded, quinolone MICs ranged between ≤0.008 and 16 μg/ml. By comparison, β-lactam MICs ranged between ≤0.008 and 16 μg/ml, with higher MICs encountered for some *S. mitis*, *S. sanguinis*, *S. mutans*, and *S. oralis* strains. Azithromycin resistance was found in all species with the exception of *S. constellatus*, and *C. hominis* and all strains except for *S. bovis* were telithromycin susceptible, with MICs of ≤1 μg/ml. All organisms except for the 5 *C. hominis* strains were inhibited by vancomycin and teicoplanin at ≤1 μg/ml, while all strains but *C. hominis* and 10 viridans group strains were inhibited by linezolid at ≤2 μg/ml (3). Quinolone resistance (defined as a levofloxacin MIC of ≥4 μg/ml) (3) was found only in two strains of *S. oralis*, one strain of *S. salivarius*, and seven *S. bovis* species, and results of analysis of resistance mechanisms can be seen in Table 2.

As described before, resistance was mostly caused by alterations in GyrA (Ser substitution at position 81) and/or ParC (Ser substitution at position 79 and Asp substitution at position 83) protein (9, 10, 18). Double substitutions in ParC and GyrA resulted in high-level resistance isolates no. 116, 124, 132, and 216, and substitution in ParC or GyrA resulted in low-level resistance for isolates no. 68, 121, 122, and 193 (9, 10, 18). To our knowledge, mutations H43D, G79C, and Y107I in GyrA and Y15D and M116I in ParC have not yet been described.

Low-level resistance in isolate no. 118 probably resulted from the presence of an efflux mechanism. Reserpine lowered the ciprofloxacin MICs in three other isolates with mutations in GyrA and ParC: no. 68, 193, and 216. Resistant isolate no. 125 had one previously undescribed mutation in ParC (Y15D); a decrease in the MIC in the presence of reserpine was not observed. This may suggest the presence of mutations in other quinolone resistance-determining regions (QRDR) or a different resistance mechanism which is not yet known in this strain. Although the presence of resistance mechanisms caused resistance to all other quinolones tested, DX-619 MICs were significantly lower (0.016 to 0.25 μg/ml). Importantly, DX-619 MICs against quinolone-resistant strains with efflux and/or defined mutations in QRDR were a few dilutions higher than those seen in quinolone-susceptible strains but in no case exceeded 0.25 μg/ml.

By comparison, β-lactam and azithromycin resistance occurred frequently. All strains except 2 of *S. bovis* were susceptible to telithromycin, and all except the 5 *C. hominis* strains were susceptible to glycopeptides and had linezolid MICs of ≤2 μg/ml, except for 10 viridans group strains which were linezolid resistant (3).

In summary, the excellent activity of DX-619 against the organisms tested in this study reflects findings by us as well as other authors of studies of DX-619 activity against quinolone-susceptible and -resistant pneumococci as well as other organisms (1, 5, 12, 17). DX-619 was also active against strains that had known mechanisms for the development of quinolone resistance. Pharmacokinetic and pharmacodynamic as well as toxicity studies will be necessary to confirm the clinical applicability of the excellent activity of DX-619 against the organisms tested.

This study was supported by a grant from Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan.

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