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Comparative Activities of Clinafloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Ofloxacin, Sparfloxacin, and Trovafloxacin and Nonquinolones Linozelid, Quinupristin-Dalfopristin, Gentamicin, and Vancomycin against Clinical Isolates of Ciprofloxacin-Resistant and -Susceptible *Staphylococcus aureus* Strains

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The activities of eight fluoroquinolones and linezolid, quinupristin-dalfopristin (Synercid), gentamicin, and vancomycin were tested against 96 ciprofloxacin-susceptible and 205 ciprofloxacin-resistant *Staphylococcus aureus* strains. Overall, clinafloxacin, followed by moxifloxacin and trovafloxacin, was the most active quinolone tested. For all isolates, linezolid and quinupristin-dalfopristin showed activities that were at least comparable to vancomycin, with no cross-resistance to any other test compound.

In recent years, the clinical efficacy of ciprofloxacin and other fluoroquinolones against infections with *Staphylococcus aureus* has been undermined by the widespread emergence of decreased susceptibility to these compounds (9). Fluoroquinolone resistance is considerably higher among methicillin-resistant *S. aureus* (MRSA) strains than among methicillin-susceptible *S. aureus* (MSSA) strains (9).

Recently, several new quinolone-derived compounds with reportedly improved activities against *S. aureus*, including MRSA, have been developed. Several studies have demonstrated superior in vitro activities by some of these new compounds (3, 5–8, 12, 15–17), although few studies have compared the activities of each together in a single test set which also includes other potential investigational antistaphylococcal drugs. In this study, we report the activities of the quinolone compounds clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin against a collection of ciprofloxacin-susceptible and -resistant *S. aureus* strains. In addition to these drugs, we also tested the susceptibilities of isolates to vancomycin, gentamicin, the investigational oxazolidinone linezolid (4), and the streptogramin compound quinupristin-dalfopristin (Synercid) (2).

Three hundred one non-repeat clinical isolates of *S. aureus* from several different institutions were studied; these comprised 50 methicillin-susceptible and 251 methicillin-resistant isolates. All isolates were confirmed as *S. aureus* by screening for the coagulase-encoding gene *coa* and for *mecA* by using a multiplex PCR (13). One hundred fifty-eight organisms isolated between 1990 and 1996 from patients residing in Germany and 36 organisms isolated between 1981 and 1989 from seven other countries—Japan ($n = 8$), Brazil ($n = 8$), Switzerland ($n = 6$), Sri Lanka ($n = 4$), Spain ($n = 4$), United Kingdom ($n = 3$), and Hungary ($n = 3$)—were selected on the basis of belonging to unique pulsed-field gel electrophoresis types (14). The remaining 112 non-repeat clinical blood isolates were isolated during 1996 and 1997 from different patients at least 5 days apart from any other isolate of the same species from the same institution, and they originated from geographically widespread hospitals in Belgium, France, Germany, Greece, Italy, The Netherlands, Spain, Portugal, and the United Kingdom.

MICs of the drugs tested were determined by an agar dilution method, according to National Committee for Clinical Laboratory Standards guidelines (11). All drugs were obtained directly from their manufacturers.

Of the 50 MSSA strains tested, 34 were susceptible to ciprofloxacin (MIC < 4 μg/ml) and demonstrated uniformly low resistance to other quinolone compounds tested (Table 1). Against these 34 MSSA strains, the most active quinolone compounds were clinafloxacin, moxifloxacin, sparfloxacin, and trovafloxacin, each demonstrating MICs at which 90% of the isolates were inhibited (MIC_{90}s) of ≤0.06 μg/ml. However, 15% (5 of 34) of ciprofloxacin-susceptible MSSA strains showed in vitro resistance to gentamicin. Against the 16 ciprofloxacin-resistant MSSA isolates, clinafloxacin, moxifloxacin and trovafloxacin were the most active quinolones, demonstrating MIC_{90}s of 1 μg/ml, with a range of ≤0.06 to 2 μg/ml. Other quinolones tested demonstrated MIC_{90}s ranging from 4 μg/ml for sparfloxacin to 8, 16, and 32 μg/ml for levofloxacin, ofloxacin, and grepafloxacin, respectively. Resistance to gentamicin was noticeably more common among ciprofloxacin-resistant MSSA isolates than among ciprofloxacin-susceptible MSSA, with 65% (11 of 17) of isolates being resistant (MICs ≥64 μg/ml), indicating an association of quinolone resistance with aminoglycoside resistance. Linezolid and vancomycin showed comparable activities against MSSA independent of ciprofloxacin susceptibility, with similar MICs for both (MIC_{90}s, 1 and 2 μg/ml, respectively; range, 0.50 to 2 μg/ml). Quinupristin-dalfopristin demonstrated the most potent activity by weight, with a MIC_{90} of 0.5 μg/ml (range, ≤0.06 to 4 μg/ml).

Sixty-two of the 251 MRSA strains tested remained susceptible to ciprofloxacin (Table 2). Against these, all of the quin-

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TABLE 1. Comparative in vitro activities of different antibiotic compounds against MSSA in relation to ciprofloxacin susceptibility

Test agent	MIC (μg/ml)					
	Ciprofloxacin-susceptible MSSA (n = 34)			Ciprofloxacin-resistant MSSA (n = 16)		
	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
Ciprofloxacin	0.12–1	0.25	0.5	4–64	16	64
Clinafloxacin	≤0.06	≤0.06	≤0.06	≤0.06–2	0.5	1
Grepafloxacin	≤0.06–0.12	≤0.06	0.12	≤0.06–32	16	32
Levofloxacin	≤0.06–0.25	0.12	0.25	0.12–16	2	8
Moxifloxacin	≤0.06	≤0.06	≤0.06	≤0.06–2	0.5	1
Ofloxacin	0.12–1	0.25	0.5	1–32	8	16
Sparfloxacin	≤0.06–0.12	≤0.06	≤0.06	≤0.06–8	0.5	4
Trovafloxacin	≤0.06	≤0.06	≤0.06	≤0.06–2	0.5	1
Gentamicin	≤0.06–128	0.5	64	0.25–>256	64	>256
Linezolid	1–2	2	2	0.5–2	1	2
Quinupristin-dalfopristin	≤0.06–4	0.5	0.5	≤0.06–2	0.5	0.5
Vancomycin	0.5–2	1	1	0.5–2	1	2

olone compounds demonstrated good activities, with MICs for all strains in the range of ≤0.06 to 2 μg/ml. Against the 189 MRSA resistant to ciprofloxacin, only clinafloxacin and moxifloxacin demonstrated in vitro activities (MIC_{90}s, 1 and 2 μg/ml, respectively) sufficiently high to suggest therapeutic potential; all other quinolone compounds had higher MIC_{90}s (range, 4 to 64 μg/ml). Gentamicin MIC_{90}s for both ciprofloxacin-susceptible and -resistant MRSA were 256 μg/ml. The percentages of MRSA fully resistant to gentamicin in ciprofloxacin-susceptible and ciprofloxacin-resistant strains were 57% (36 of 62) and 77% (147 of 189), clearly demonstrating the association of quinolone and aminoglycoside resistance. In contrast, susceptibilities to linezolid, quinupristin-dalfopristin, and vancomycin remained independent of ciprofloxacin susceptibility, with these drugs having comparable activities (MIC_{90}s, 1 to 2 μg/ml).

Worldwide emerging resistance to ciprofloxacin in clinically significant gram-positive organisms, in particular *S. aureus* and *Streptococcus pneumoniae*, has prompted the development of new quinolones mostly derived by further modifications of the core quinolone structure. Some of the newer compounds tested here clearly demonstrate improved in vitro activities against *S. aureus*. This is particularly so for clinafloxacin and moxifloxacin, by virtue of the fact that all isolates tested, several of which had ciprofloxacin MICs of >256 μg/ml, demonstrated clinafloxacin and moxifloxacin MIC_{90}s of ≤2 μg/ml. Overall, against all *S. aureus* strains tested, the most active quinolone compounds were clinafloxacin and moxifloxacin, followed by trovafloxacin, sparfloxacin, levofloxacin, grepafloxacin, and ofloxacin.

TABLE 2. Comparative in vitro activities of different antibiotic compounds against MRSA in relation to ciprofloxacin susceptibility

Test agent	MIC (μg/ml)					
	Ciprofloxacin-susceptible MRSA (n = 62)			Ciprofloxacin-resistant MRSA (n = 189)		
	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
Ciprofloxacin	0.12–2	0.25	1.0	4–>256	32	64
Clinafloxacin	≤0.06–0.12	≤0.06	≤0.06	≤0.06–4	0.5	1
Grepafloxacin	≤0.06–0.12	≤0.06	≤0.06	≤0.06–64	16	32
Levofloxacin	≤0.06–0.5	0.12	0.25	1–64	4	16
Moxifloxacin	≤0.06–0.12	≤0.06	≤0.06	≤0.06–4	2	2
Ofloxacin	0.12–1	0.25	0.5	1–64	16	32
Sparfloxacin	≤0.06–1	≤0.06	0.12	≤0.06–64	4	16
Trovafloxacin	≤0.06–0.5	≤0.06	≤0.06	≤0.06–8	1	4
Gentamicin	0.12–>256	64	256	≤0.06–>256	64	256
Linezolid	0.5–2	1	2	0.12–2	1	2
Quinupristin-dalfopristin	≤0.06–4	0.5	1	≤0.06–4	0.5	1
Vancomycin	0.12–2	1	1	0.5–2	1	2

Against *S. aureus*, linezolid clearly demonstrates an in vitro activity equal to that of vancomycin, with no *S. aureus* isolates having linezolid MICs greater than 2 μg/ml. In addition to this in vitro potency, linezolid possesses other promising features, most noticeably its lack of cross-resistance with any other mechanisms. Linezolid has been shown to possess a mechanism of action unique among gram-positive organisms by inhibiting protein synthesis by binding to the 50S ribosomal subunit (10). While a larger range of MICs was recorded for quinupristin-dalfopristin (≤0.06 to 4 μg/ml), the MIC_{90} remained at least comparable and mostly better than the MIC_{90}s of all other nonquinolones tested, with no cross-resistance to any other drug tested. The streptogramin subunits quinupristin and dalfopristin act synergistically to inhibit protein synthesis and have been previously shown to be active against *S. aureus* (1). In light of the invariable multidrug-resistant nature of MRSA and the possible emergence of vancomycin-refractory staphylococcal isolates, linezolid and quinupristin-dalfopristin are particularly interesting compounds for further evaluation.

In summary, comparison of the activities of clinafloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin against ciprofloxacin-susceptible and -resistant MSSA and MRSA strains shows that, overall, clinafloxacin, moxifloxacin, and trovafloxacin demonstrate the best in vitro potencies against even highly ciprofloxacin-resistant MRSA. The investigational oxazolidinone linezolid and the new streptogramin quinupristin-dalfopristin showed activities that were better than or comparable to vancomycin, with no cross-resistance to any other compound.

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