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Comparative In Vitro Activities of Trovafloxacin (CP-99,219) against 445 Gram-Positive Isolates from Patients with Endocarditis and Those with Other Bloodstream Infections

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The in vitro activity of trovafloxacin (CP-99,219), a new fluoroquinolone, was compared with the in vitro activities of other commonly used quinolones and other antimicrobial agents against 445 gram-positive microorganisms isolated between 1986 and 1995 from patients with endocarditis and those with other bloodstream infections. The MICs at which 90% of the isolates are inhibited (MIC_{90}) of trovafloxacin for methicillin-susceptible staphylococci, viridans group streptococci, and enterococci were 0.06, 0.25, and 0.5 mg/liter, respectively. The MIC_{90} of trovafloxacin for vancomycin-resistant enterococci as well as for methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible and ciprofloxacin-resistant *S. aureus*, isolated from sources other than blood, was 1 mg/liter. For the quinolones the rank order of activity was trovafloxacin > sparfloxacin > ciprofloxacin = ofloxacin > pefloxacin. Depending on the species tested, trovafloxacin was 4- to 64-fold more active than ciprofloxacin. Further experimental and in vivo studies are warranted to evaluate the efficacy of trovafloxacin in the treatment of bacterial endocarditis and other infections caused by gram-positive organisms.

Quinolones represent a major class of antimicrobial agents and are derivatives of nalidixic acid, which was introduced in the 1960s. The fluoroquinolones, introduced in the late 1970s, are synthetically developed agents which are used worldwide to treat a wide range of infections (22). Ciprofloxacin, ofloxacin, and pefloxacin are examples of these very potent compounds, which have markedly improved activities compared to earlier quinolones (29). Although they are highly active against gram-negative microorganisms, failures in the treatment of serious infections caused by gram-positive organisms have been encountered (13, 14, 26). Further developments have produced newly synthesized agents, like sparfloxacin and temafloxacin, with improved activities against staphylococci and streptococci (1, 5). The structure-activity relationship for the quinolone agents has recently been reviewed (9). The substitution of an alkylated pyrrolidine at the 7 position of the molecule greatly enhances activity against gram-positive microorganisms. Trovafloxacin (CP-99,219) is such a newly developed compound (11).

The objective of this study was to compare the in vitro activities of trovafloxacin and other relevant antimicrobial agents against gram-positive isolates from patients with endocarditis and those with other bloodstream infections.

A total of 445 gram-positive microorganisms isolated from blood were tested in this study. Of these, 355 strains were isolated between 1986 and 1988 from patients with endocarditis in The Netherlands (27). Another 90 viridans group streptococci were isolated between 1990 and 1995 from hospitalized patients with endocarditis or other bloodstream infections at the University Hospital of Rotterdam. In addition, we tested 20 vancomycin-resistant enterococci (VRE) harboring the *vanA* gene, 13 methicillin-resistant *Staphylococcus aureus* (MRSA) organisms harboring the *mecA* gene, 13 ciprofloxacin-resistant but methicillin-susceptible *S. aureus* (MSSA) organisms, and 19 ciprofloxacin-resistant and coagulase-negative staphylococci (CoNS). These strains were isolated from sources other than blood. All MRSA organisms and VRE were unique and epidemiologically unrelated strains. All staphylococci (n = 123) and β-hemolytic streptococci (n = 11) were identified by standard methods as described previously (21, 25). All viridans group streptococci (n = 276) and enterococci (n = 35) were identified with the API 32 rapid system by following the instructions of the manufacturer (Biomerieux, Marcy l'Etoile, France). The strains belonged to the following species or groups: MSSA (n = 87), CoNS (n = 36), *Enterococcus faecalis* (n = 35), β-hemolytic streptococci (n = 11), *Streptococcus oralis* (n = 62), *Streptococcus mitis* (n = 56), "*Streptococcus milleri*" (n = 25), *Streptococcus gordonii* (n = 23), *Streptococcus bovis* (n = 20), *Streptococcus mutans* (n = 18), and other viridans group streptococci (n = 72). The following antibiotics were tested: trovafloxacin (Pfizer bv, Capelle aan de IJssel, The Netherlands [NL]), sparfloxacin and pefloxacin (Rhone-Poulenc-Rorer, Amstelveen, NL), ciprofloxacin (Bayer bv, Mijdrecht, NL), ofloxacin (Hoechst Roussel bv, Hoevelaken, NL), vancomycin (Eli-Lilly, Nieuwegein, NL), teicoplanin and penicillin (Yamanouchi Pharma, Leiderdorp, NL), and amoxicillin and flucloxacillin (SmithKline Beecham, Rijswijk, NL). All in vitro experiments were performed by the agar dilution method according to the recommendations of the National Committee for Clinical Laboratory Standards (23). The following media were used: for staphylococci and enterococci, Mueller-Hinton medium (Difco, Amsterdam, NL); and for β-hemolytic streptococci and viridans group streptococci, Mueller-Hinton medium supplemented with 5% sheep blood. The final inoculum was approximately 10^4 CFU per spot. *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *Streptococ-*

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TABLE 1. In vitro activities of trovafloxacin (CP-99,219) and other agents against 455 gram-positive organisms from patients with endocarditis and those with other bloodstream infections

Microorganism (no. of strains)	Antibiotic	MIC (mg/liter)		
		Range	50%	90%
MSSA (87)	Trovafloxacin	0.015–1	0.03	0.06
	Sparfloxacin	0.015–8	0.06	0.125
	Ciprofloxacin	0.125–128	0.5	1
	Ofloxacin	0.125–16	0.25	0.5
	Pefloxacin	0.25–64	0.5	1
	Penicillin	0.03–>2	>2	>2
	Flucloxacillin	0.125–1	0.25	0.5
	Vancomycin	0.5–2	1	1
	Teicoplanin	0.5–2	1	2
CoNS (36)	Trovafloxacin	<0.008–0.125	0.06	0.06
	Sparfloxacin	0.03–0.5	0.06	0.125
	Ciprofloxacin	<0.015–2	0.25	0.5
	Ofloxacin	<0.008–1	0.5	0.5
	Pefloxacin	0.25–2	0.5	1
	Penicillin	0.03–>2	0.5	>2
	Flucloxacillin	0.06–8	0.25	2
	Vancomycin	0.5–4	2	2
	Teicoplanin	<0.125–16	1	4
E. faecalis (35)	Trovafloxacin	0.015–0.5	0.25	0.5
	Sparfloxacin	0.06–1	0.5	1
	Ciprofloxacin	0.25–4	1	2
	Ofloxacin	0.25–16	4	8
	Pefloxacin	0.125–8	4	8
	Amoxicillin	<0.06–32	0.5	4
	Vancomycin	1–8	1	4
	Teicoplanin	0.125–1	0.5	1
Viridans group streptococci (276)	Trovafloxacin	<0.008–>128	0.125	0.25
	Sparfloxacin	0.03–32	0.5	1
	Ciprofloxacin	0.125–64	2	8
	Ofloxacin	<0.008–32	2	4
	Pefloxacin	0.015–>128	16	64
	Penicillin	0.008–16	0.06	0.5
	Amoxicillin	0.008–>16	0.06	0.5
	Vancomycin	0.06–8	1	2
	Teicoplanin	<0.015–16	0.25	0.25
β-Hemolytic streptococci (11)	Trovafloxacin	0.125–0.25	0.125	0.25
	Sparfloxacin	0.25–0.5	0.5	0.5
	Ciprofloxacin	0.5–1	0.5	1
	Ofloxacin	1–8	4	8
	Pefloxacin	4–32	8	16
	Penicillin	0.03–0.06	0.06	0.06
	Amoxicillin	<0.015–0.5	0.06	0.06
	Vancomycin	0.5–1	0.5	1
	Teicoplanin	<0.06–0.25	0.25	0.25

cus pneumoniae ATCC 40619 were used as control strains. All media were incubated for 18 h in 5% CO_2. The MIC was defined as the lowest concentration of the drug that prevented visible growth.

The in vitro activities of trovafloxacin, four other fluoroquinolones, and four other relevant antimicrobial agents against 455 isolates from patients with endocarditis or other bloodstream infections are shown in Tables 1 and 2.

The MICs at which 90% of the isolates are inhibited (MIC_{90}) of trovafloxacin for the staphylococcal isolates (MSSA and CoNS) were ≤0.06 mg/liter (Table 1). The MIC_{90} of sparfloxacin for staphylococci was 1 twofold dilution higher than that of trovafloxacin. The MICs of ciprofloxacin and ofloxacin were 8- to 16-fold higher than the MICs of trovafloxacin. However, this group of organisms, isolated from patients with endocarditis and those with other bloodstream infections, contained no MRSA organisms and only two ciprofloxacin-resistant *S. aureus* organisms, reflecting the low prevalence of these resistant organisms in The Netherlands. Therefore, 13 MRSA organisms isolated from sources other than blood were collected and tested. Trovafloxacin was 8- to 64-fold more active than ciprofloxacin against these MRSA organisms and inhibited 90% of the strains at 1 mg/liter, in contrast to the MIC_{90} of trovafloxacin for the methicillin-susceptible isolates of ≤0.06 mg/liter (Tables 1 and 3). The in vitro activity of trovafloxacin against MRSA has previously been evaluated by others (15, 20). In those studies, the MIC_{90} of trovafloxacin for ciprofloxacin-resistant and -susceptible MRSA varied from <0.125 to 128 mg/liter (MIC_{50}, 8 mg/liter) and 0.03 to 0.125 mg/liter (MIC_{50}, 0.062 mg/liter), respectively, 8- to 64-fold lower than the MIC_{90} of ciprofloxacin. It is important to note that those studies did not include ciprofloxacin-resistant MSSA. We report here that 90% of the ciprofloxacin-resistant MSSA were inhibited by a MIC of trovafloxacin of 1 mg/liter, 32-fold lower than that of ciprofloxacin (Table 3).

The frequency at which spontaneous mutations arise, resulting in resistance to trovafloxacin, has been studied for *S. aureus* and *S. pneumoniae* (2, 16). Exposure of *S. aureus* to a concentration of trovafloxacin of 0.12 mg/liter failed to select resistant mutants (2). However, at trovafloxacin concentrations of ≥0.5 mg/liter, resistant mutants of *S. pneumoniae* arose at a frequency of $\leq 9.1 \times 10^{-9}$ (16). At comparable factors above the MICs of ciprofloxacin and trovafloxacin, the frequencies of mutation in *S. pneumoniae* appeared to be similar for the two fluoroquinolones (16). Furthermore, mutants resistant to ciprofloxacin or trovafloxacin at concentrations of ≥10 times the MIC could not be obtained (16). In view of its anticipated tissue concentrations and its greater in vitro activity against *S. aureus* and *S. pneumoniae*, trovafloxacin might be less likely than ciprofloxacin to select resistance in these microorganisms in vivo (2). Therefore, on the basis of these in vitro studies, trovafloxacin appears to be an interesting drug for the treatment of infection with ciprofloxacin-susceptible MRSA. Although trovafloxacin is clearly more active against ciprofloxacin-resistant staphylococci than ciprofloxacin, it may not show sufficient activity against all ciprofloxacin-resistant staphylococci to warrant its clinical use in the treatment of infections with this resistant organism.

Ninety percent of the enterococci were inhibited by 0.5 mg of trovafloxacin per liter, 1 mg of sparfloxacin per liter, and 2 mg of ciprofloxacin per liter. The activities against 20 VRE from sources other than blood are presented in Table 3. Ninety percent of those were inhibited by 1 mg of trovafloxacin per liter and 4 mg of ciprofloxacin per liter. A breakpoint of 2 mg/liter for susceptibility to trovafloxacin has recently been proposed (7). The MICs for all VRE were ≤2 mg/liter, in contrast to the study by Cormican and Jones (7), which comprised 150 VRE and reported only 37% of these VRE to be susceptible to 2 mg of trovafloxacin per liter. However, our data are more in concordance with those of Coque et al., who reported 80% of VRE to be susceptible to 2 mg of trovafloxacin per liter (6). In summary, trovafloxacin shows increased activity compared to that of ciprofloxacin against most vancomycin-susceptible enterococci and some VRE and, therefore, might be considered for the treatment of enterococcal infections.

The MIC_{90} of trovafloxacin and sparfloxacin for the viridans group streptococci were 0.25 and 1 mg/liter, respectively. The MIC_{90} of ofloxacin and ciprofloxacin for these organisms, how-

TABLE 2. In vitro activities of trovafloxacin (CP-99,219) and other agents against 204 well-defined viridans group streptococcal species from patients with endocarditis and those with other bloodstream infections

Microorganism (no. of strains)	Antibiotic	MIC (mg/liter)		
		Range	50%	90%
S. oralis (62)	Trovafloxacin	0.015–0.5	0.125	0.25
	Sparfloxacin	0.125–2	0.5	2
	Ciprofloxacin	0.5–32	4	16
	Ofloxacin	0.5–16	4	4
	Pefloxacin	4–128	32	64
	Penicillin	0.008–8	0.03	0.25
	Amoxicillin	0.008–2	0.03	0.25
	Vancomycin	0.06–2	0.5	1
	Teicoplanin	0.03–4	0.25	0.25
S. mitis (56)	Trovafloxacin	0.03–4	0.125	0.5
	Sparfloxacin	0.125–32	0.5	2
	Ciprofloxacin	1–64	2	8
	Ofloxacin	1–32	2	16
	Pefloxacin	0.25–128	16	32
	Penicillin	<0.015–4	0.06	1
	Amoxicillin	<0.015–8	0.06	0.5
	Vancomycin	0.5–8	1	2
	Teicoplanin	0.015–16	0.125	0.25
"S. milleri" (25)	Trovafloxacin	<0.008–0.5	0.125	0.5
	Sparfloxacin	0.25–2	0.5	1
	Ciprofloxacin	0.5–16	2	8
	Ofloxacin	1–16	2	4
	Pefloxacin	0.5–32	8	16
	Penicillin	0.008–1	0.06	0.06
	Amoxicillin	0.008–1	0.125	0.25
	Vancomycin	0.5–2	1	2
	Teicoplanin	0.03–0.25	0.125	0.25
S. gordonii (23)	Trovafloxacin	0.03–1	0.125	0.25
	Sparfloxacin	0.03–0.5	0.25	0.5
	Ciprofloxacin	0.5–4	2	4
	Ofloxacin	0.25–4	2	2
	Pefloxacin	4–64	16	32
	Penicillin	<0.015–16	<0.015	0.5
	Amoxicillin	<0.015–>16	0.06	0.5
	Vancomycin	0.5–2	1	1
	Teicoplanin	0.06–8	0.25	2
S. bovis (20)	Trovafloxacin	0.125–0.5	0.25	0.25
	Sparfloxacin	0.125–2	0.5	2
	Ciprofloxacin	2–4	2	4
	Ofloxacin	4	4	4
	Pefloxacin	16–64	32	64
	Penicillin	0.03–2	0.06	0.06
	Amoxicillin	0.06–8	0.06	0.25
	Vancomycin	0.5–1	0.5	0.5
	Teicoplanin	0.125–1	0.25	0.5
S. mutans (18)	Trovafloxacin	<0.008–0.5	0.125	0.25
	Sparfloxacin	0.125–16	0.5	2
	Ciprofloxacin	1–4	2	4
	Ofloxacin	<0.008–4	2	4
	Pefloxacin	8–128	32	32
	Penicillin	<0.015–0.25	0.03	0.06
	Amoxicillin	<0.015–0.25	0.03	0.125
	Vancomycin	0.5–2	1	2
	Teicoplanin	<0.015–2	0.125	1

TABLE 3. In vitro activities of trovafloxacin (CP-99,219) and ciprofloxacin against VRE, MRSA, ciprofloxacin-resistant MSSA, and ciprofloxacin-resistant CoNS isolated from sources other than blood

Microorganism (no. of strains)	Antibiotic	MIC (mg/liter)		
		Range	50%	90%
VRE (20)	Trovafloxacin	0.125–2	0.5	1
	Ciprofloxacin	0.5–16	2	4
MRSA (13)	Trovafloxacin	0.008–1	0.25	1
	Ciprofloxacin	0.125–64	4	16
MSSA (13)	Trovafloxacin	0.06–1	0.5	1
	Ciprofloxacin	4–32	16	32
CoNS (19)	Trovafloxacin	0.5–8	0.5	4
	Ciprofloxacin	2–64	16	64

ever, were 16- and 32-fold higher, respectively, than the MIC_{90} of trovafloxacin. This is in agreement with recent reports (6, 11). The MICs for 204 clearly defined species within the viridans group streptococci are shown in Table 2. We found higher rates of penicillin resistance among *S. mitis* isolates than among isolates of other species of viridans group streptococci. This has previously been reported by others (3, 8). Trovafloxacin inhibited 90% of the β-hemolytic streptococci at concentrations of ≤0.25 mg/liter, 2-, 4-, and 32-fold less than the MIC_{90} of sparfloxacin, ciprofloxacin, and ofloxacin, respectively.

Depending on the species tested, trovafloxacin was two- to eightfold more active than sparfloxacin and 4- to 64-, 8- to 32-, and 16- to 256-fold more active than ciprofloxacin, ofloxacin, and pefloxacin, respectively.

The emergence of high rates of penicillin resistance in viridans group streptococci has recently been reported in Europe and in the United States (4, 8, 17). In our study, 1.5% of the viridans group streptococci were highly resistant to penicillin (MICs, ≥4 mg/liter). For 17.5% of the strains the MICs of penicillin were 0.125 to 2 mg/liter (i.e., intermediate resistance). Ninety percent of the penicillin-susceptible (MICs, ≤0.06 mg/liter) viridans group streptococci were inhibited by trovafloxacin concentrations of ≤0.25 mg/liter. The MIC_{90} of trovafloxacin for the intermediately resistant and highly resistant viridans group streptococci were ≤0.25 mg/liter and therefore identical to the MIC_{90} for the penicillin-susceptible strains. The MICs of trovafloxacin for the four viridans group streptococci that were highly resistant to penicillin (MICs, 4 to 16 mg/liter) were 0.06 to 0.25 mg/liter.

The recent emergence of penicillin resistance may have implications for the therapy as well as the prophylaxis of infections with viridans group streptococci, e.g., endocarditis and bacteremia (8, 18). In this respect, the increased activity of trovafloxacin against penicillin-susceptible as well as penicillin-resistant viridans group streptococci is promising. Clinical experience in the treatment of endocarditis with fluoroquinolones, however, is limited to the use of ciprofloxacin and rifampin in patients with right-sided staphylococcal endocarditis (10, 19). These studies report high success rates for combination therapy that includes ciprofloxacin. However, the emergence of resistance to ciprofloxacin and rifampin during the treatment of right-sided *S. aureus* endocarditis has been described (14, 26). Treatment regimens involving oral administration of quinolones have been used for treatment of experimental enterococcal endocarditis with variable success (24, 28, 30). Also in an experimental setting, sparfloxacin was found to be an effective drug for the treatment of endocarditis due to penicillin-susceptible as well as penicillin-resistant viridans group streptococci (12). These reports, together with the pre-

sented data, suggest the importance of further experimental and clinical evaluation of the efficacy of trovafloxacin in the treatment of bacterial endocarditis and other infections caused by gram-positive microorganisms.

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