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Activities of Clinafloxacin, Alone and in Combination with Other Compounds, against 45 Gram-Positive and -Negative Organisms for Which Clinafloxacin MICs Are High

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Time-kill studies indicated that clinafloxacin showed synergy after 24 h with ceftazidime, amikacin, and imipenem against 12, 8, and 10 of 33 gram-negative rods, respectively; with vancomycin, teicoplanin, cefotaxime, and amikacin against 3, 3, 1, and 1 of 9 staphylococci and enterococci, respectively; and with vancomycin, penicillin, and cefotaxime against 0, 2, and 2 of 3 pneumococci, respectively. The MICs of clinafloxacin alone for most strains were ≥1 μg/ml.

Clinafloxacin is a quinolone active against a wide array of gram-positive and -negative aerobes and anaerobes (3–9, 11, 13–17). In a previous study that used a provisional clinafloxacin breakpoint of 1.0 μg/ml, 100% of ciprofloxacin-susceptible strains and 63% of ciprofloxacin-resistant strains were susceptible to clinafloxacin (9).

The activities of quinolones may be enhanced when they are combined with other agents (1, 2, 19–21). This study employed time-kill testing to evaluate the possible synergy between clinafloxacin and a range of other compounds against 45 gram-positive and -negative strains requiring high clinafloxacin MICs that were selected from our previous study (9). Where possible, three strains from each species for which the clinafloxacin MICs were 1.0, 2.0, and 4.0 μg/ml were chosen. Where this was not possible, strains that required the highest clinafloxacin MICs were tested.

Agar dilution MIC determinations (9) were performed on Mueller-Hinton agar (supplemented with 5% sheep blood for pneumococci) according to standardized methods (18). Time-kill assays (10) were used to test the activity of clinafloxacin alone and in combination with a variety of agents against the 45 strains (Tables 1 to 3). For the time-kill assays, strains were grown in cation-adjusted Mueller-Hinton broth (supplemented with 5% lysed horse blood for pneumococci). Antimicrobials (alone and in combination) were added to tubes at the MIC, 1 dilution above the MIC, and 2 dilutions below the MIC. Drug-free controls were also included. In all cases (confirmed by duplicate testing), at least one drug in a combination did not significantly affect the organisms growth curves when used alone. Tubes were inoculated with 60-μl volumes containing 5×10^5 to 5×10^6 CFU of the test organism per ml and incubated at 35°C in a shaking water bath. At 0, 6, 12, and 24 h, 0.1-ml aliquots were removed from each tube, and viability counts were performed on blood agar plates. For *Proteus mirabilis*, MacConkey agar was used to avoid the problem of swarming. Synergy was considered achieved when there was a ≥2-$\log_{10}$ decrease in CFU per milliliter between the drug combination and its most active constituent after 6, 12, and 24 h and the number of surviving organisms in the presence of the combination was ≥2 $\log_{10}$ CFU/ml below the number of the starting inoculum (10). Because of trailing endpoints, the presence of synergy between clinafloxacin and ceftazidime against the two *P. mirabilis* strains could not be determined.

In all cases, the MICs obtained by agar and broth macrodilution differed by a maximum of 1 dilution. The MICs of drugs alone, as well as the results of synergy time-kill studies, are presented in Tables 1 to 3. As can be seen, with the exception of one *Acinetobacter* sp., three pneumococci, and one *Enterococcus faecium* strain, strains were chosen because the clinafloxacin MICs for them are high.

Time-kill studies showed that clinafloxacin demonstrated synergy after 24 h with ceftazidime, amikacin, and imipenem against 12, 8, and 10 of 33 gram-negative rods, respectively; with vancomycin, teicoplanin, cefotaxime, and amikacin against 3, 3, 1, and 1 of 9 staphylococci and enterococci, respectively; with vancomycin, penicillin, and cefotaxime against 0, 2, and 2 of 3 pneumococci, respectively. In most cases of synergy at earlier time periods, regrowth occurred, but no common trends in growth with the same antimicrobial combinations occurred.

When synergy at 6, 12, and 24 h was compared for individual organisms, clinafloxacin was found to be synergistic with ceftazidime, amikacin, and imipenem against, respectively, 2, 2, and 3 of 3 strains of *Pseudomonas aeruginosa*; 3, 0, and 1 of 3 strains of *Stenotrophomonas maltophilia*; 2, 3, and 3 of 3 strains of *Acinetobacter* spp.; 3, 2, and 3 of 3 strains of *Burkholderia cepacia*; 0, 2, and 1 of 3 strains of *Escherichia coli*; 1, 1, and 1 of 3 strains of *Klebsiella pneumoniae*; 1, 1, and 0 of 3 strains of *Enterobacter cloacae*; 0, 0, and 0 of 1 strain of *Enterobacter aerogenes*; 3, 3, and 3 of 3 strains of *Citrobacter freundii*; 3, 3, and 2 of 3 strains of *Serratia marcescens*; 2, 2, and 2 of 2 strains of *Providencia stuartii*; and 1, 0, and 0 of 1 *Morganella morganii* strain. As stated above, synergy between clinafloxacin and ceftazidime for *P. mirabilis* could not be determined, but clinafloxacin was synergistic with amikacin and imipenem against 0 and 2 of 2 *P. mirabilis* strains.

Clinafloxacin showed synergy with vancomycin, teicoplanin, cefotaxime, and amikacin against 2, 3, 3, and 2 of 3 methicillin-resistant strains of *Staphylococcus aureus*; 2, 1, 1, and 0 of 3 strains of *Enterococcus faecalis*; and 1, 1, 1, and 1 of 3 strains of *E. faecium* (the only strain for which the clinafloxacin MIC was low [0.25 μg/ml]). Additionally, 1 of 3 methicillin-resistant *S. aureus* strains (second strain in Table 2) showed synergy be-

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TABLE 1. Results of synergy testing with gram-negative organisms

Organism	MIC (μg/ml)				Result for drug combination at time (h)[a]								
					Clinafloxacin + ceftazidime			Clinafloxacin + amikacin			Clinafloxacin + imipenem		
	Clinafloxacin	Ceftazidime	Amikacin	Imipenem	6	12	24	6	12	24	6	12	24
P. aeruginosa	1	>128	>64	32	Sy (0.25/32)	Ad	Ad	Sy (0.25/8)	Ad	Ad	Ad	Sy (0.25/2)	Ad
	2	>128	>64	128	Ad	Sy (0.25/32)	Ad	Ad	Sy (0.25/32)	Ad	Ad	Sy (0.25/64)	Ad
	2	64	8	4	Ad	Ad	Ad	Ad	Ad	Ad	Sy (0.25/0.5)	Ad	Ad
S. maltophilia	2	128	>64	>128	Ad	Sy (0.25/16)	Sy (0.25/16)	Ad	Ad	Ad	Ad	Sy (0.25/64)	Sy (0.25/64)
	1	>128	32	>128	Ad	Sy (0.5/32)	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	1	128	32	>128	Ad	Sy (1/32)	Ad	Ad	Ad	Ad	Ad	Ad	Ad
Acinetobacter spp.	4	8	4	0.25	Sy (0.5/2)	Ad	Ad	Sy (0.5/1)	Ad	Ad	Sy (0.5/0.06)	Ad	Ad
	4	32	2	0.5	Ad	Ad	Ad	Ad	Sy (1/1)	Ad	Ad	Sy (1/0.12)	Sy (1/0.12)
	0.25	8	4	0.25	Ad	Ad	Sy (0.06/2)	Ad	Sy (0.06/1)	Sy (0.06/1)	Ad	Sy (0.06/0.06)	Ad
B. cepacia	2	4	>64	16	Ad	Sy (0.5/2)	Sy (0.5/2)	Ad	Sy (0.5/32)	Sy (0.5/32)	Ad	Ad	Sy (0.5/8)
	4	2	32	64	Ad	Sy (2/1)	Ad	Ad	Ad	Ad	Sy (2/32)	Sy (2/32)	Sy (2/32)
	2	8	>64	128	Ad	Ad	Sy (0.5/2)	Ad	Ad	Sy (0.5/16)	Sy (0.5/32)	Sy (0.5/32)	Sy (0.5/32)
E. coli	2	0.125	2	0.125	Ad	Ad	Ad	Sy (0.5/1)	Ad	Ad	Ad	Ad	Ad
	1	0.25	4	0.06	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	4	64	32	0.5	Ad	Ad	Ad	Ad	Sy (2/16)	Ad	Sy (2/0.25)	Sy (2/0.25)	Ad
K. pneumoniae	1	0.5	1	0.06	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Sy (0.25/0.03)
	4	>128	1	0.25	Ad	Sy (1/32)	Sy (1/32)	Ad	Sy (1/0.5)	Ad	Ad	Ad	Ad
	8	1	1	0.125	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
E. cloacae	2	8	2	1	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	4	8	2	0.125	Ad	Ad	Ad	Ad	Sy (2/1)	Ad	Ad	Ad	Ad
	1	0.5	2	0.5	Sy (0.12/0.12)	Ad	Sy (0.12/0.12)	Ad	Ad	Ad	Ad	Ad	Ad
E. aerogenes	2	1	2	4	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
C. freundii	2	1	2	0.125	Ad	Sy (0.5/0.5)	Ad	Ad	Sy (0.5/1)	Sy (0.5/1)	Ad	Sy (0.5/0.06)	Ad
	1	64	2	0.25	Sy (0.25/16)	Ad	Ad	Ad	Sy (0.25/0.5)	Ad	Sy (0.25/0.12)	Ad	Ad
	1	64	2	0.25	Ad	Sy (0.25/16)	Sy (0.25/16)	Ad	Sy (0.25/1)	Sy (0.25/1)	Ad	Sy (0.25/0.12)	Sy (0.25/0.12)
S. marcescens	4	1	4	2	Ad	Sy (1/0.12)	Sy (1/0.12)	Ad	Sy (1/2)	Sy (1/2)	Ad	Ad	Ad
	0.5	1	2	2	Ad	Sy (0.12/0.25)	Sy (0.12/0.25)	Ad	Sy (0.12/1)	Ad	Ad	Sy (0.12/0.5)	Sy (0.12/0.5)
	1	0.5	2	1	Sy (0.25/0.12)	Sy (0.25/0.12)	Ad	Sy (0.25/1)	Sy (0.25/1)	Ad	Ad	Sy (0.25/0.25)	Sy (0.25/0.25)
P. mirabilis	2	ND	16	8	ND	ND	ND	Ad	Ad	Ad	Ad	Sy (0.5/1)	Sy (0.5/1)
	0.5	ND	16	8	ND	ND	ND	Ad	Ad	Ad	Ad	Sy (0.12/0.5)	Sy (0.12/0.5)
P. stuartii	1	0.25	1	1	Sy (0.25/0.06)	Ad	Sy (0.25/0.06)	Sy (0.25/0.25)	Ad	Sy (0.25/0.25)	Ad	Sy (0.25/0.5)	Sy (0.25/0.5)
	2	0.5	2	0.5	Sy (0.5/0.06)	Sy (0.5/0.06)	Sy (0.5/0.06)	Ad	Sy (0.5/1)	Sy (0.5/1)	Ad	Ad	Sy (0.5/0.12)
M. morganii	8	>128	8	2	Sy (1/4)	Ad	Sy (1/4)	Ad	Ad	Ad	Ad	Ad	Ad

[a] Sy, synergistic; Ad, additive. Values in parentheses are MICs, i.e., the lowest concentrations (in micrograms per milliliter) of each compound that yielded a ≥2-$\log_{10}$ decrease in CFU per milliliter compared to the more active single compound. ND, not done because of trailing endpoints.

TABLE 3. Results of synergy testing with *Streptococcus pneumoniae*[a]

MIC (μg/ml)					Result for drug combination at time (h)[b]											
Clinafloxacin	Vancomycin	Penicillin	Cefotaxime	Quinupristin-dalfopristin	Clinafloxacin + vancomycin			Clinafloxacin + penicillin			Clinafloxacin + cefotaxime			Clinafloxacin + quinupristin-dalfopristin		
					6	12	24	6	12	24	6	12	24	6	12	24
0.12	0.25	4	2	0.5	Ad	Ad	Ad	Ad	Ad	Sy (0.03/2)	Ad	Ad	Sy (0.03/1)	Ad	Ad	Ad
0.12	0.25	4	2	0.5	Ad	Ad	Ad	Ad	Ad	Sy (0.06/2)	Ad	Sy (0.06/1)	Sy (0.06/1)	Ad	Ad	Ad
0.12	0.25	4	1	0.5	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad

[a] Three strains were tested.
[b] Sy, synergistic; Ad, additive. Values in parentheses are MICs, i.e., indicate the lowest concentrations (in micrograms per milliliter) of each compound that yielded a ≥2-$\log_{10}$ decrease in CFU per milliliter compared to the more active single compound.

TABLE 2. Results of synergy testing with methicillin-resistant *S. aureus* and enterococci

Organism	MIC (μg/ml)					Result for drug combination at time (h)[a]											
	Clina-floxacin	Vanco-mycin	Teico-planin	Cefo-taxime	Ami-kacin	Clinafloxacin + vancomycin			Clinafloxacin + teicoplanin			Clinafloxacin + cefotaxime			Clinafloxacin + amikacin		
						6	12	24	6	12	24	6	12	24	6	12	24
S. aureus	2	1	0.5	>64	8	Ad	Sy (1/0.5)	Sy (1/0.5)	Sy (1/0.25)	Sy (1/0.25)	Sy (1/0.25)	Ad	Sy (1/128)	Sy (1/128)	Ad	Sy (1/4)	Sy (1/4)
	4	0.5	1	>64	4	Ad	Ad	Ad	Ad	Sy (2/0.5)	Ad	Ad	Sy (2/128)	Sy (2/128)	Ad	Ad	Ad
	1	1	0.5	>64	8	Ad	Sy (0.25/0.5)	Sy (0.25/0.5)	Ad	Sy (0.25/0.25)	Sy (0.25/0.25)	Ad	Sy (0.25/32)	Sy (0.25/32)	Ad	Sy (0.25/4)	Ad
E. faecalis	4	1	0.25	>64	64	Ad	Sy (1/0.5)	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	1	1	0.12	>64	64	Ad	Ad	Ad	Ad	Sy (0.5/0.06)	Ad	Sy (0.5/>64)	Ad	Ad	Ad	Ad	Ad
	2	1	0.25	>64	>64	Sy (1/0.5)	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
E. faecium	8	>64	>8	>64	>64	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad
	0.25	1	0.25	>64	8	Ad	Sy (0.12/0.5)	Sy (0.12/0.5)	Ad	Sy (0.12/0.12)	Sy (0.12/0.12)	Sy (0.12/256)	Sy (0.12/256)	Sy (0.12/256)	Sy (0.12/4)	Sy (0.12/4)	Ad
	8	>64	>8	>64	32	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad	Ad

[a] Sy, synergistic; Ad, additive. Values in parentheses are MICs, i.e., the lowest concentrations (in micrograms per milliliter) of each compound that yielded a ≥2-$\log_{10}$ decrease in CFU per milliliter compared to the more active single compound.

tween clinafloxacin (2 μg/ml) and quinupristin-dalfopristin (0.125 μg/ml) (data not shown) after 24 h. Clinafloxacin showed synergy with vancomycin, penicillin G, cefotaxime, and quinupristin-dalfopristin against 0, 2, 2, and 0 of 3 strains of pneumococci. In all cases of synergy, clinafloxacin MICs were lower than those obtained with clinafloxacin alone, and, in most cases, sub-MICs of the accompanying drug were also found. In four gram-negative rods (one strain of *P. aeruginosa*, one strain of *S. maltophilia*, and two strains of *B. cepacia*), two strains of methicillin-resistant *S. aureus*, one strain of *E. faecalis*, and one strain of *E. faecium*, synergy was obtained with sub-MICs of clinafloxacin only when concentrations of imipenem (gram-negatives) or cefotaxime (gram-positives) of >16.0 and >64 μg/ml, respectively, were used. No antagonistic results were found by time-kill methods, and in many cases, bacterial concentrations in synergistic combinations fell to threshold levels (300 colonies) (10).

In this study, we documented synergy by time-kill methods between sub-MICs of clinafloxacin and a variety of other agents against a spectrum of gram-negative and -positive bacteria. Some degree of synergy at 6, 12, or 24 h was observed with most strains. The synergy between clinafloxacin and ceftazidime against *S. maltophilia* reflects previous findings (2, 19–21). The synergy between clinafloxacin and either penicillin G or cefotaxime against pneumococci may be clinically relevant. We attempted to test quinolone-resistant strains, but the rapid lysis of these strains precluded analysis (data not shown). Quinolone-resistant pneumococci are currently rare, but they may increase with the widespread use of newer quinolones with expanded activity against gram-positive organisms. Synergy between clinafloxacin and β-lactams against pneumococci may help in the treatment of bacterial meningitis, where lower MICs as well as drug penetration into cerebrospinal fluid are of particular importance (12) and where even a twofold difference between the MIC of clinafloxacin alone and in combination may be therapeutically significant.

Few members of each species were tested in this study, and results require confirmation with larger numbers of strains of each species. However, equivalent synergies between clinafloxacin and ceftazidime against *S. maltophilia* and between clinafloxacin and other agents against other nonfermenters, such as *P. aeruginosa* and the acinetobacters, reflect findings by members of our group with trovafloxacin and levofloxacin (19–21).

The clinical significance of synergy at periods earlier than 24 h is unclear. However, Eliopoulos and Moellering have stated that synergy may be defined at an earlier time period, as long as the MIC of the compound(s) in combination falls within levels achievable in blood (10). This was the case for most strains tested; however, in four gram-negative nonfermentative rods and four gram-positive cocci, synergy was demonstrated in vitro between sub-MICs of clinafloxacin and concentrations of imipenem and cefotaxime, respectively, which are not clinically achievable. The significance of this finding is unknown. Results of the present study require confirmation in a clinical setting.

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