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Activities of Three Quinolones, Alone and in Combination with Extended-Spectrum Cephalosporins or Gentamicin, against *Stenotrophomonas maltophilia*

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The present study examined the activities of trovafloxacin, levofloxacin, and ciprofloxacin, alone and in combination with cefoperazone, ceftazidime, cefpirome, and gentamicin, against 100 strains of *Stenotrophomonas maltophilia* by the MIC determination method and by synergy testing of the combinations by the time-kill and checkerboard titration methods for 20 strains. The respective MICs at which 50% and 90% of isolates were inhibited for the drugs used alone were as follows: trovafloxacin, 0.5 and 2.0 μg/ml; levofloxacin, 2.0 and 4.0 μg/ml; ciprofloxacin, 4.0 and 16.0 μg/ml; cefoperazone, >128.0 and >128.0 μg/ml; ceftazidime, 32.0 and >128.0 μg/ml; cefpirome, >128.0 and >128.0 μg/ml; and gentamicin, 128.0 and >128.0 μg/ml. Synergistic fractional inhibitory concentration indices (≤0.5) were found for ≥50% of strains for trovafloxacin-cefoperazone, trovafloxacin-ceftazidime, levofloxacin-cefoperazone, levofloxacin-ceftazidime, ciprofloxacin-cefoperazone, and ciprofloxacin-ceftazidime, with other combinations affecting fewer strains. For 20 strains tested by the checkerboard titration and time-kill methods, synergy (≥100-fold drop in count compared to the count achieved with the more active compound) was more pronounced after 12 h due to regrowth after 24 h. At 12 h, trovafloxacin at 0.004 to 0.5 μg/ml showed synergy with cefoperazone for 90% of strains, with ceftazidime for 95% of strains with cefpirome for 95% of strains, and with gentamicin for 65% of strains. Levofloxacin at 0.03 to 0.5 μg/ml and ciprofloxacin at 0.5 to 2.0 μg/ml showed synergy with cefoperazone for 80% of strains, with ceftazidime for 90 and 85% of strains, respectively, with cefpirome for 85 and 75% of strains, respectively, and with gentamicin for 65 and 75% of strains, respectively. Time-kill assays were more discriminatory than checkerboard titration assays in demonstrating synergy for all combinations.

Infections with *Stenotrophomonas maltophilia* are increasingly encountered, especially in immunocompromised patients (5, 6, 8–10, 18). This organism is inherently resistant to most β-lactam and non-β-lactam agents by virtue of permeability barriers and the elaboration of at least two β-lactamases (2, 3, 7, 14, 15); trimethoprim-sulfamethoxazole, ticarcillin-clavulanate, or a combination of these pairs of compounds are suggested as the treatments of choice for infections caused by this organism (12, 13). β-Lactam resistance is mediated by the production of at least two β-lactamases: a zinc-dependent metalloenzyme which breaks down carbapenems and which is resistant to β-lactamase inhibitors and a cephalosporinase which is susceptible to β-lactamase inhibitors (2, 3, 7, 14, 15).

The activities of quinolones against *S. maltophilia* strains vary. Previous studies in our laboratory have documented that the MICs at which 50% (MIC_{50}s) and 90% (MIC_{90}s) for trovafloxacin and levofloxacin are 1.0 and 2.0 μg/ml, respectively, and 2.0 and 4.0 μg/ml, respectively (16, 17). Preliminary results of a recent study (17) also suggested synergistic activity between trovafloxacin and ceftazidime against these strains.

In order to confirm and extend the findings presented above, the current study examined the effects of trovafloxacin, levofloxacin, and ciprofloxacin combined with cefoperazone, ceftazidime, cefpirome, and gentamicin against a spectrum of *S. maltophilia* strains.

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MATERIALS AND METHODS

Bacteria and antimicrobials agents. The bacterial strains used in this study were all recent clinical isolates (one isolate per patient) that had been identified by standard methods (12) and were stored in double-strength litmus milk (Difco Laboratories, Detroit, Mich.) at −70°C until use. Antimicrobial powders for susceptibility testing were obtained from their respective manufacturers.

MIC and checkerboard titration assays. MIC and checkerboard titration assays were performed with 100 strains in microtiter trays with cation-supplemented Mueller-Hinton broth (Difco) (1, 4, 17). Trovafloxacin, levofloxacin, and ciprofloxacin were tested at 11 concentrations each (0.016 to 16.0 μg/ml), while cefoperazone, ceftazidime, cefpirome, and gentamicin were tested at 7 concentrations each (2.0 to 128.0 μg/ml). The trays were prepared with a 96-channel dispenser and were stored at −70°C until use. The quinolones were dispensed alone in the first row and were combined with cephalosporins or gentamicin in the remaining rows. Cefoperazone, ceftazidime, cefpirome, and gentamicin were also dispensed alone in the first column. Inocula were prepared by suspending growth from blood agar plates in sterile saline to a density equivalent to that of a 0.5 McFarland standard and were diluted 1:10 to produce a final inoculum of 5×10^5 CFU/ml. The trays were incubated aerobically overnight. Standard quality control strains were included with each run. Fractional inhibitory concentrations (FICs) were calculated as the MIC of drug A or B in combination/MIC of drug A or B alone, and the FIC index was obtained by adding the two

TABLE 1. Microdilution MICs of the compounds tested

Drug	MIC (μg/ml)		
	Range	50%	90%
Trovafloxacin	0.03–16.0	0.5	2.0
Levofloxacin	0.25–>16.0	2.0	4.0
Ciprofloxacin	0.5–>16.0	4.0	16.0
Cefoperazone	2.0–>128.0	>128.0	>128.0
Ceftazidime	2.0–>128.0	32.0	>128.0
Cefpirome	4.0–>128.0	>128.0	>128.0
Gentamicin	2.0–>128.0	128.0	>128.0

TABLE 2. Results of checkerboard titrations[a]

Combination	% Strains for which the FIC indices were as follows:	
	≤0.5	>0.5–4
Trovafloxacin + cefoperazone	58	42
Trovafloxacin + ceftazidime	58	42
Levofloxacin + cefoperazone	54	46
Levofloxacin + ceftazidime	50	50
Ciprofloxacin + cefoperazone	58	42
Ciprofloxacin + ceftazidime	50	50
Trovafloxacin + cefpirome	35	65
Trovafloxacin + gentamicin	11	89
Levofloxacin + cefpirome	35	65
Levofloxacin + gentamicin	11	89
Ciprofloxacin + cefpirome	35	65
Ciprofloxacin + gentamicin	20	80

[a] No strains for which FIC indices were >4.0 were found.

FICs. FIC indices were interpreted as synergistic if the values were ≤0.5, additive or indifferent if the values were >0.5 to 4, and antagonistic if the values were >4.0 (1, 4, 17).

Time-kill determinations. Twenty strains were empirically chosen from our collection to represent a cross-section of isolates with representative antibiograms and were tested by the time-kill method as described previously (1). All compounds were tested alone and in the same combinations used in the checkerboard titration assays. In each case, concentrations up to four times above and down to at least four times below the MICs were tested. Viability count studies were performed at 0, 6, 12, and 24 h. Drug carryover was addressed by dilution as described previously (1, 17). Regrowth of each strain occurred at 24 h in the presence of all three quinolones; most strains were resistant de novo to the cephalosporins and gentamicin (see Table 3). No attempt was made to further characterize the clones resistant at 24 h. Because of this regrowth, synergy was defined as a ≥100-fold decrease in the viable count at 12 h for organisms treated with the combination at 12 h compared to the viable count in the presence of the more active of the two compounds used alone (4).

RESULTS

The respective MIC_{50}s and MIC_{90}s of the agents tested are listed in Table 1 and were as follows: trovafloxacin, 0.5 and 2.0 μg/ml; levofloxacin, 2.0 and 4.0 μg/ml; ciprofloxacin, 4.0 and 16.0 μg/ml; cefoperazone, >128.0 and >128.0 μg/ml; ceftazidime, 32.0 and >128.0 μg/ml; cefpirome, >128.0 and >128.0 μg/ml; and gentamicin, 128.0 and >128.0 μg/ml. Of the 100 strains tested by the checkerboard titration method (Table 2), synergistic FIC indices (≤0.5) were found for ≥50% of strains with trovafloxacin-cefoperazone, trovafloxacin-ceftazidime, levofloxacin-cefoperazone, levofloxacin-ceftazidime, ciprofloxacin-cefoperazone, and ciprofloxacin-ceftazidime, with the other combinations affecting fewer strains.

For 20 strains tested by the checkerboard titration and time-kill methods (Tables 3 and 4), synergy (≥100-fold drop in the count compared to that after treatment with the more active compound) was more pronounced after 12 h due to regrowth after 24 h. At 12 h trovafloxacin at 0.004 to 0.5 μg/ml showed synergy with cefoperazone for 90% of strains, with ceftazidime for 95% of strains, with cefpirome for 95% of strains, and with gentamicin for 65% of strains. Levofloxacin at 0.03 to 0.5 μg/ml and ciprofloxacin at 0.5 to 2.0 μg/ml showed synergy with cefoperazone for 80% of strains, with ceftazidime for 90 and 85% of strains, respectively, with cefpirome for 85 and 75% of strains, respectively, and with gentamicin for 65 and 75% of strains, respectively. With the exception of two strains (strain 60 with trovafloxacin-cefoperazone and strain 51 with ciprofloxacin-cefoperazone), for all strains against which the drugs were synergistic by the checkerboard titration method, the drugs were also found to be synergistic by the time-kill method. However, in many cases time-kill studies showed synergy while an additive or indifferent effect was found by the checkerboard titration method (Table 4). In cases of synergy between quinolones and other compounds, the MICs of the quinolones in synergistic combinations were lower than those of the compounds used alone. The MICs of β-lactams and gentamicin in synergistic combinations also tended to be lower (Table 4).

The least synergy was found against strains 32, 60, 65, 68, 73, and 90 by the time-kill method. The different combinations did not consistently fail to show synergy against the strains, and no consistent pattern emerged. Similar resistance phenotypes were observed with the same cephalosporin, regardless of the quinolone used in the combination: cephalosporin MICs in synergistic combinations ranged between 1.0 and 128.0 μg/ml (Table 4).

TABLE 3. MICs of drugs tested alone in time-kill tests for synergy

Strain	MIC (μg/ml)						
	Trovafloxacin	Levofloxacin	Ciprofloxacin	Cefoperazone	Ceftazidime	Cefpirome	Gentamicin
51	0.5	1.0	4.0	>128.0	>128.0	>128.0	>128.0
52	1.0	4.0	8.0	>128.0	32.0	>128.0	>128.0
56	4.0	4.0	16.0	>128.0	>128.0	>128.0	>128.0
57	0.25	1.0	2.0	>128.0	>128.0	>128.0	>128.0
55	0.125	0.25	0.25	>128.0	>128.0	>128.0	32.0
60	0.06	0.5	1.0	>128.0	16.0	>128.0	>128.0
2	0.5	1.0	2.0	>128.0	4.0	128.0	128.0
27	1.0	4.0	16.0	>128.0	128.0	>128.0	>128.0
28	0.5	0.5	2.0	>128.0	128.0	>128.0	32.0
30	1.0	1.0	2.0	>128.0	128.0	128.0	128.0
32	2.0	2.0	4.0	>128.0	>128.0	>128.0	>128.0
61	0.125	0.5	1.0	16.0	4.0	128.0	64.0
65	0.06	0.25	2.0	>128.0	8.0	128.0	64.0
68	0.06	0.5	2.0	16.0	4.0	64.0	>128.0
70	0.25	2.0	4.0	>128.0	>128.0	>128.0	>128.0
73	1.0	2.0	8.0	>128.0	128.0	>128.0	>128.0
75	0.25	2.0	8.0	8.0	4.0	>128.0	16.0
77	0.25	2.0	4.0	≤2.0	8.0	128.0	8.0
82	0.5	1.0	2.0	>128.0	16.0	>128.0	128.0
106	0.03	0.25	0.5	≤2.0	4.0	8.0	16.0

TABLE 4. Results of time-kill studies for synergy

Strain	Trovafloxacin + cefoperazone		Trovafloxacin + ceftazidime		Levofloxacin + cefoperazone		Levofloxacin + ceftazidime		Ciprofloxacin + cefoperazone		Ciprofloxacin + ceftazidime		Trovafloxacin + cefpirome		Trovafloxacin + gentamicin		Levofloxacin + cefpirome		Levofloxacin + gentamicin		Ciprofloxacin + cefpirome		Ciprofloxacin + gentamicin	
	C[a]	T[b]	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T
51	A	0.12/32	A	0.12/32	S	0.25/32	A	0.25/32	S	A	A	A	A	0.12/64	A	0.12/32	A	0.25/64	A	0.25/32	A	1/64	A	1/32
52	A	0.12/64	S	0.12/8	S	0.5/64	S	0.5/8	S	1/128	S	1/16	A	0.12/64	A	0.12/64	A	0.5/64	A	0.5/64	A	A	A	1/128
56	S	0.5/64	S	0.5/128	A	0.5/64	S	0.5/128	A	A	A	2/128	S	0.5/128	A	0.5/64	A	0.5/128	A	0.5/64	A	2/128	A	2/64
57	A	0.03/128	S	0.03/128	A	0.25/128	A	0.25/128	A	0.5/128	A	0.5/128	S	0.03/64	A	0.03/64	A	0.25/64	A	0.25/64	A	0.5/64	A	0.5/64
55	A	0.06/64	S	0.06/64	A	0.12/64	S	0.12/64	A	0.25/64	S	0.25/64	S	0.06/16	A	0.06/16	A	0.12/16	A	0.12/16	A	0.25/16	A	0.12/16
60	S	A	S	0.016/2	A	A	S	0.06/2	A	A	S	0.25/2	S	0.016/64	S	0.016/32	S	0.06/64	S	0.06/32	A	0.25/64	S	0.25/32
2	A	0.12/32	A	0.12/1	A	0.25/32	A	0.25/1	A	0.5/32	A	0.5/1	A	0.12/8	A	0.12/2	A	A	A	0.25/2	A	0.5/8	A	0.5/2
27	S	0.12/64	S	0.12/32	S	0.5/64	S	0.5/32	S	1/64	S	1/32	S	0.12/64	A	0.12/32	S	0.5/64	A	0.5/32	S	1/64	A	1/32
28	A	0.06/64	S	0.06/32	A	0.12/64	A	0.12/32	S	0.5/64	S	0.5/32	S	0.06/64	A	A	A	0.12/64	A	0.5/32	A	0.5/64	A	0.5/1
30	S	0.12/32	S	0.12/16	S	0.25/32	S	0.25/16	S	0.5/32	S	0.5/16	S	0.12/32	S	0.12/8	S	0.25/32	S	0.25/8	S	0.5/32	S	0.5/8
32	A	0.12/32	S	0.12/16	A	0.25/32	A	0.25/16	A	0.5/32	A	0.5/16	S	0.12/32	A	A	A	0.25/32	A	A	A	A	A	A
61	S	0.03/1	A	0.03/2	A	A	A	0.12/2	S	0.12/1	A	0.25/2	A	0.03/16	A	A	S	0.12/16	A	A	A	0.25/16	S	0.25/1
65	A	0.016/16	A	0.016/8	A	A	A	0.06/8	S	0.25/16	A	0.25/8	A	0.016/16	A	A	A	0.06/16	A	A	S	0.25/16	A	A
68	S	0.016/8	A	A	A	0.5/8	A	0.5/4	S	0.25/8	A	A	A	A	A	0.016/32	A	0.5/16	A	0.5/32	S	0.25/16	A	A
70	A	0.06/128	A	0.06/128	A	0.25/128	A	0.25/128	A	0.5/128	A	0.5/128	A	0.06/64	A	A	A	0.25/64	A	A	A	0.5/64	A	A
73	S	0.12/16	S	0.12/16	S	0.5/16	A	A	S	0.5/16	S	0.5/16	S	0.12/16	A	A	A	0.5/16	A	A	A	A	A	A
75	S	0.016/0.25	S	0.016/1	S	0.12/1	A	0.12/0.25	A	1/1	A	1/0.25	S	0.016/8	S	0.016/0.25	A	A	A	0.12/0.25	A	1/8	S	1/0.25
77	A	0.016/1	A	0.016/4	A	0.12/1	A	0.12/4	A	0.5/1	A	0.5/4	A	0.016/64	A	0.016/0.25	A	A	A	A	A	A	A	0.5/0.25
82	A	0.25/64	S	0.25/4	A	0.5/64	S	0.5/4	A	1/64	S	1/4	A	0.25/64	A	A	A	0.5/64	A	A	A	1/64	A	1/32
90	A	A	A	0.004/0.25	A	A	A	A	A	A	A	A	A	0.004/1	A	0.004/2	S	0.03/1	A	0.03/2	A	A	S	0.06/2

[a] C, checkerboard titration; S, synergy; A, additivity or indifference.

[b] T, time-kill method; the lowest concentration (in micrograms per milliliter) of each compound in the combination yielding sustained bactericidal activity (≥100-fold decrease in viable count) at 12 h compared to the concentration (in micrograms per milliliter) of the more active drug. A, additive.

DISCUSSION

The results of the current study confirm that the MICs of trovafloxacin and levofloxacin cluster around the susceptibility breakpoints of ≤2.0 μg/ml which have been approved for levofloxacin and established provisionally for trovafloxacin (11), while the MICs of ciprofloxacin are higher. High cephalosporin and gentamicin MICs reflect permeability barriers and, in the case of the β-lactams, the effect of the production of multiple β-lactamases (2, 3, 7, 14, 15). Because infections with *S. maltophilia* are usually serious in nature and often occur in immunosuppressed patients, high-dose parenteral therapy is recommended (5, 6, 8–10, 18).

Checkerboard titrations have been shown to be less discriminatory than time-kill testing for the detection of synergy against *Streptococcus pneumoniae*, members of the family *Enterobacteriaceae*, and gram-negative, nonfermenting bacteria. It should also be noted that checkerboard titrations reveal bacteriostatic activity only, while the time-kill method tests for both bacteriostatic and bactericidal activities (1, 17). In a previous study from our laboratory, checkerboard titration failed to demonstrate significant synergy between levofloxacin and amikacin against *Acinetobacter* spp. By contrast, time-kill testing showed synergy between the two compounds at subinhibitory concentrations of levofloxacin for all strains for which levofloxacin MICs were ≤2.0 μg/ml (1). Thus, time-kill testing, although more labor-intensive, may be a more discriminatory method of demonstrating synergy.

Eliopoulos and Moellering (4) have stated that for strains such as *S. maltophilia* which demonstrate regrowth at 24 h, synergy may be defined at an earlier time period, e.g., 12 h (4), as long as the MIC of the compound(s) in the combination falls within the levels achievable in blood. For this reason, we feel that the synergy results at 12 h may be clinically relevant.

In the current study, checkerboard titrations demonstrated similar rates of synergy (50 to 58%) for combinations of all three quinolones with cefoperazone and ceftazidime. Lower rates of synergy (11 to 35%) were observed when quinolones were combined with cefpirome and gentamicin. Time-kill tests showed that at trovafloxacin and levofloxacin concentrations of ≤0.5 μg/ml, synergy was obtained with β-lactams against 16 to 19 of the 20 strains tested. The concentrations of trovafloxacin and levofloxacin in the combinations were lower than their individual MICs when they were used alone and are easily achievable clinically. The National Committee for Clinical Laboratory Standards (11) has approved levofloxacin susceptibility breakpoints of ≤2.0 μg/ml for aerobic organisms, and trovafloxacin susceptibility breakpoints of ≤1.0 and 2.0 μg/ml for pneumococci and anaerobes, respectively. By contrast, the MICs of ciprofloxacin in synergistic combinations, although lower than the MICs of ciprofloxacin used alone, clustered around the susceptibility breakpoint for this agent (≤1.0 μg/ml) (11).

Given the tendency of *S. maltophilia* strains to develop resistance on exposure to antimicrobial agents (reflected by regrowth in time-kill experiments after 24 h), the clinical significance of the synergy observed in the current study is unknown. An animal model is being developed to investigate this phenomenon further. Clinical studies are required to test the relevance of our findings, but these will be difficult to perform, given the infrequency with which *S. maltophilia* can definitely be implicated as a cause of human infection rather than colonization. Additionally, the influence of the failure of quinolone–β-lactam and quinolone-gentamicin combinations to demonstrate synergy at 24 h on the once-daily dosing of trovafloxacin and levofloxacin is unknown. Further studies are also needed to

compare the in vitro synergy between quinolones and extended-spectrum cephalosporins and between quinolones and gentamicin with the synergy previously described between trimethoprim-sulfamethoxazole and ticarcillin-clavulanate (13). Clinical testing will determine whether these quinolones will have to be administered more frequently than once daily if they are to be used in synergistic combinations against this organism. However, we feel that the results of this study indicate that a combination of trovafloxacin or levofloxacin with cefoperazone, ceftazidime, cefpirome, or perhaps, gentamicin represents an alternate therapeutic modality to trimethoprim-sulfamethoxazole and/or ticarcillin-clavulanate.

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