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NOTES

Susceptibilities of Bacterial Isolates from Patients with Cancer to Levofloxacin and Other Quinolones

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The antibacterial activity of levofloxacin was compared with those of ofloxacin and ciprofloxacin against bacterial isolates from patients with cancer. In general, levofloxacin was as active or was twofold more active than ofloxacin and was two- to fourfold less active than ciprofloxacin against most gram-negative pathogens. Against *Pseudomonas aeruginosa*, ciprofloxacin was the most active agent tested (MIC for 90% of isolates tested, 1.0 μg/ml). Overall, all three agents had similar activities against gram-positive organisms and were moderately active against methicillin-susceptible *Staphylococcus aureus* and coagulase-negative staphylococci, *Streptococcus* species, and *Enterococcus* species.

During the past decade a large number of newer quinolones have been developed. Most of these agents, including norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, and fleroxacin, have broader antimicrobial spectra and improved bioavailabilities in comparison with those of naladixic acid (16). Some have been used for infection prevention and for the treatment of established infections in neutropenic cancer patients (2, 6, 10, 15). More recently, broad-spectrum quinolones such as ciprofloxacin, which are available for parenteral and oral administration, have made it possible to shorten the duration of antibiotic administration to febrile cancer patients in the hospital by facilitating the early discharge of such patients on oral antibiotic therapy (3). Certain low-risk neutropenic patients have even been treated as outpatients during the entire febrile episode (12). These newer applications have widened the scope of the quinolones as antibacterial agents. However, the widespread prophylactic and therapeutic usage of quinolones in neutropenic cancer patients has raised concern about the emergence of resistance to them and a reduction in their overall impact as clinically useful antibiotics.

Ofloxacin exists as two optically active isomers because of the asymmetric center at C-3 of the oxazine ring, and levofloxacin (*l*-ofloxacin) is the more active isomer (4, 5, 14). We compared the in vitro activity of levofloxacin with those of ofloxacin and ciprofloxacin against clinical bacterial isolates obtained from patients with cancer being treated at our institution. The following antimicrobial agents were obtained in the form of standard powders for laboratory use from the indicated manufacturers: ciprofloxacin, Miles Pharmaceuticals, West Haven, Conn.; and ofloxacin and levofloxacin, Robert Wood Johnson Pharmaceutical Research Institute, Raritan, N.J. These powders were kept frozen at −70°C until use. A total of 666 organisms were tested. All organisms were isolated from patients admitted to the University of Texas M. D. Anderson Cancer Center at Houston during the past 5 years. The majority (>90%) of these isolates were from blood culture specimens, and the rest were from various clinical sources including sputum, wounds, urine, bile, and cerebrospinal fluid. Many isolates came from patients who had received cephalosporins, penicillins, carbapenems, monobactams, and quinolones for therapy or prophylaxis. Only one isolate per patient was used for testing in order to avoid duplication. *Staphylococcus aureus* and *Staphylococcus epidermidis* isolates were considered penicillin G susceptible on the basis of an MIC of <0.1 μg/ml, methicillin susceptible on the basis of an MIC of ≤4.0 μg/ml, and methicillin resistant on the basis of an MIC of ≥8.0 μg/ml.

Susceptibility testing was performed in accordance with the guidelines established by the National Committee for Clinical Laboratory Standards by using a previously described microtiter broth dilution method (8, 11). Briefly, organisms were inoculated into broth and were incubated overnight at 37°C. Appropriate dilutions were made so that the final inoculum tested was 5×10^5 CFU/ml. The test medium used was cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) for all organisms except *Corynebacterium jeikeium*, which was tested in brain heart infusion broth with 5% rabbit serum, and the streptococci, which were tested in cation-adjusted Mueller-Hinton broth with 2% lysed horse blood. Antibiotic concentrations were prepared manually, with serial twofold dilutions ranging from 64.0 to 0.03 μg/ml, and were dispensed automatically with an MIC-2000 apparatus (Dynatech Laboratories, Inc., Alexandria, Va.). *Staphylococcus aureus* ATCC 25933, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used as control strains to ensure the validity of the results. The MIC was defined as the lowest concentration of each antimicrobial agent that inhibited visible growth after 16 to 20 h of incubation at 35°C.

The overall results are shown in Table 1. Levofloxacin inhibited 90% of isolates of *Acinetobacter calcoaceticus* subsp. *lwoffii*, *Aeromonas hydrophila*, *Citrobacter* spp., *Enterobacter cloacae*, *Enterobacter agglomerans*, *Escherichia coli*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Salmonella* spp., *Serratia marcescens*,

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TABLE 1. Comparative in vitro activities of levofloxacin against gram-negative bacteria

Organism (no. of strains)	Antimicrobial agent	MIC (μg/ml)[a]			% Susceptible[b]
		50%	90%	Range	
Alcaligenes denitrificans subsp. *xylosoxidans* (15)	Ciprofloxacin	0.25	32.0	0.25–32.0	53
	Levofloxacin	0.50	8.0	0.12–8.0	
	Ofloxacin	0.50	8.0	0.25–8.0	60
Acinetobacter anitratus (20)	Ciprofloxacin	0.12	1.0	≤0.03–16.0	90
	Levofloxacin	0.12	0.50	≤0.03–8.0	
	Ofloxacin	0.12	0.25	0.06–8.0	95
Acinetobacter lwoffii (20)	Ciprofloxacin	0.06	0.25	≤0.03–0.25	100
	Levofloxacin	0.06	0.25	≤0.03–0.25	
	Ofloxacin	0.25	0.50	0.06–0.5	100
Aeromonas hydrophila (10)	Ciprofloxacin	≤0.03	0.25	≤0.03–0.50	100
	Levofloxacin	≤0.03	0.25	≤0.03–1.0	
	Ofloxacin	≤0.03	0.50	≤0.03–2.0	100
Citrobacter diversus (10)	Ciprofloxacin	≤0.03	0.06	≤0.03–0.06	100
	Levofloxacin	0.06	0.12	≤0.03–0.25	
	Ofloxacin	0.06	0.25	≤0.03–0.50	100
Citrobacter freundii (15)	Ciprofloxacin	0.06	0.12	≤0.03–0.12	100
	Levofloxacin	0.12	0.25	0.06–0.50	
	Ofloxacin	0.25	0.50	0.12–0.50	100
Enterobacter aerogenes (25)	Ciprofloxacin	≤0.03	2.0	≤0.03–2.0	84
	Levofloxacin	0.06	4.0	≤0.03–4.0	
	Ofloxacin	0.12	8.0	0.06–8.0	84
Enterobacter cloacae (25)	Ciprofloxacin	≤0.03	0.12	≤0.03–1.0	100
	Levofloxacin	0.06	0.25	≤0.03–1.0	
	Ofloxacin	0.06	0.50	≤0.03–2.0	100
Enterobacter agglomerans (10)	Ciprofloxacin	≤0.03	0.06	≤0.03–0.50	100
	Levofloxacin	0.06	0.12	≤0.03–0.50	
	Ofloxacin	0.12	0.25	≤0.03–1.0	100
Escherichia coli (50)	Ciprofloxacin	≤0.03	0.12	≤0.03–32	94
	Levofloxacin	≤0.03	0.12	≤0.03–32	
	Ofloxacin	0.06	0.12	≤0.03–64	92
Klebsiella pneumoniae (30)	Ciprofloxacin	≤0.03	0.25	≤0.03–2.0	93
	Levofloxacin	0.06	0.50	≤0.03–4.0	
	Ofloxacin	0.12	1.0	0.06–8.0	90
Klebsiella oxytoca (20)	Ciprofloxacin	≤0.03	≤0.03	≤0.03–8.0	95
	Levofloxacin	0.06	0.12	≤0.03–8.0	
	Ofloxacin	0.06	0.12	≤0.03–16.0	95
Proteus mirabilis (25)	Ciprofloxacin	≤0.03	≤0.03	≤0.03–0.06	100
	Levofloxacin	0.06	0.06	0.06–0.12	
	Ofloxacin	0.12	0.12	0.06–0.12	100
Pseudomonas aeruginosa (50)	Ciprofloxacin	0.12	1.0	≤0.03–4.0	90
	Levofloxacin	0.50	4.0	0.06–16.0	
	Ofloxacin	0.50	8.0	0.06–16.0	86
Pseudomonas putida (10)	Ciprofloxacin	0.25	0.50	0.06–0.50	100
	Levofloxacin	1.0	4.0	0.50–4.0	
	Ofloxacin	2.0	8.0	0.50–8.0	70
Pseudomonas fluorescens (10)	Ciprofloxacin	0.25	0.50	0.06–0.50	100
	Levofloxacin	0.25	2.0	0.12–2.0	
	Ofloxacin	0.50	4.0	0.25–4.0	70
Xanthomonas maltophilia (25)	Ciprofloxacin	2.0	8.0	0.50–>64	44
	Levofloxacin	1.0	8.0	0.25–>64	
	Ofloxacin	1.0	8.0	0.25–>64	64

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TABLE 1—*Continued*

Organism (no. of strains)	Antimicrobial agent	MIC (μg/ml)[a]			% Susceptible[b]
		50%	90%	Range	
Salmonella spp. (10)	Ciprofloxacin	≤0.03	≤0.03	≤0.03–0.12	100
	Levofloxacin	0.06	0.25	≤0.03–0.25	
	Ofloxacin	0.06	0.12	0.06–0.25	100
Serratia marcescens (25)	Ciprofloxacin	0.06	0.12	≤0.03–0.25	100
	Levofloxacin	0.12	0.12	0.06–0.50	
	Ofloxacin	0.25	0.50	0.06–1.0	100
Morganella morganii (10)	Ciprofloxacin	≤0.03	≤0.03	≤0.03–0.50	100
	Levofloxacin	≤0.03	0.12	≤0.03–0.50	
	Ofloxacin	0.06	0.12	0.06–1.0	100

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.
[b] Breakpoints used to determine the percentage of susceptible isolates were 1.0 μg/ml for ciprofloxacin and 2.0 μg/ml for ofloxacin. Susceptibility breakpoints for levofloxacin have not yet been accepted by the National Committee for Clinical Laboratory Standards.

and *Morganella morganii* at a concentration of 0.25 μg/ml. *Alcaligenes denitrificans* subsp. *xylosoxidans* and *Xanthomonas maltophilia* isolates were relatively resistant, with MICs of levofloxacin for 90% of isolates tested being 8.0 μg/ml. Levofloxacin was moderately active against *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, and *Pseudomonas putida*, inhibiting 88, 88, 90, and 80% of isolates, respectively, at a concentration of 2.0 μg/ml. Overall, against most gram-negative isolates, levofloxacin was two- to fourfold less active than ciprofloxacin and was twofold more active than ofloxacin. Against *Pseudomonas aeruginosa*, still an important and frequent pathogen in neutropenic cancer patients, ciprofloxacin was four- to eightfold more active than levofloxacin and ofloxacin.

Greater than 90% of methicillin-susceptible *Staphylococcus aureus* isolates were susceptible to 1.0 μg of all three quinolones per ml, with levofloxacin being marginally more active than ofloxacin and ciprofloxacin (Table 2). However, for more than 75% of methicillin-resistant *Staphylococcus aureus* isolates, >2.0 μg of each agent per ml was required for inhibition. All ciprofloxacin-resistant methicillin-resistant *Staphylococcus aureus* isolates were also resistant to ofloxacin and levofloxacin. All three agents were moderately active against methicillin-susceptible *Staphylococcus epidermidis* and *Staphylococcus hominis* isolates, inhibiting 90 and 80% of the isolates, respectively, at a concentration of 1.0 μg/ml. However, all methicillin-resistant *Staphylococcus epidermidis* isolates and most *Staphylococcus haemolyticus* isolates were resistant to all three agents. Marginal differences were noted in the activities of all three agents against beta-hemolytic *Streptococcus* spp., with >90% being susceptible to 2.0 μg of each drug per ml. Levofloxacin appeared to be more active against *Streptococcus pneumoniae* isolates, inhibiting 100% of the isolates at a concentration of 2.0 μg/ml, whereas 80 and 55% of the isolates were inhibited by ciprofloxacin and ofloxacin, respectively, at the same concentration. The activities of all three agents against alpha-hemolytic *Streptococcus* spp. were variable, with a few isolates being inhibited by concentrations of ≤0.03 μg/ml and other isolates requiring 4.0 to 64.0 μg/ml for inhibition. All three agents were moderately active against *Enterococcus* spp., whereas most *Listeria monocytogenes* and *Corynebacterium jeikeium* isolates were resistant to all three agents. Overall, all three drugs had similar activities against gram-positive organisms, and no single agent could be considered superior to the other two.

Our results are consistent with those published by Fu et al. (4), who compared the activity of levofloxacin with those of various antimicrobial agents, including ciprofloxacin and ofloxacin. In that study (4), as in ours, levofloxacin was found to be two- to fourfold less active than ciprofloxacin against most gram-negative isolates, including *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*, which are the most frequently isolated gram-negative pathogens from neutropenic cancer patients (4). It was two- to fourfold more active than ciprofloxacin against *Xanthomonas maltophilia*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* isolates. Also, as in our study, levofloxacin was as active or was twofold more active than ofloxacin against most organisms tested. Despite heavy antimicrobial usage in cancer patients, the majority of our isolates (with the exception of methicillin-resistant *Staphylococcus* spp.) did not show greater overall resistance to the quinolones than those tested by Fu et al. (4), which were obtained from various clinical laboratories throughout the United States. These data indicate that the newer quinolones, including levofloxacin, continue to have potent activity against most important gram-negative pathogens.

Numerous clinical applications have been found for the newer quinolones in neutropenic cancer patients. Agents such as norfloxacin and ciprofloxacin are used in most large cancer treatment centers for antimicrobial prophylaxis in high-risk patients with prolonged neutropenia, including patients with acute leukemia and recipients of bone marrow transplantations (2, 4, 15). Ciprofloxacin has also been used in combination with various agents (aminoglycosides, beta-lactams, vancomycin, and clindamycin) for the treatment of febrile episodes in neutropenic patients, both in the hospital and in an ambulatory care setting (1, 3, 10, 12, 13). Among the currently available quinolones, ciprofloxacin is the most potent, particularly against gram-negative bacilli, including *Pseudomonas aeruginosa*, and any promising newer agents belonging to this class need to be compared with ciprofloxacin. Our data indicate that against a large number of recent clinical isolates obtained from cancer patients, levofloxacin was not superior to ciprofloxacin in its overall antibacterial activity. Levofloxacin does, however, possess some potential advantages. It has been shown to achieve higher concentrations than ciprofloxacin in the serum and kidneys of mice, indicating a more favorable pharmacokinetic profile (4). Also, in animal model studies of pyelonephritis and systemic infections, levofloxacin was more efficacious than ciprofloxacin against *Staphylococcus aureus* and was as efficacious or was slightly more efficacious than ciprofloxacin against *Escherichia coli*, *Klebsiella pneumoniae*,

TABLE 2. Comparative in vitro activities of levofloxacin against gram-positive bacteria

Organism (no. of strains)	Antimicrobial agent	MIC (μg/ml)[a]			% Susceptible[b]
		50%	90%	Range	
Staphylococcus aureus, penicillin susceptible (20)	Ciprofloxacin	0.25	0.50	0.06–2.0	95
	Levofloxacin	0.12	0.25	0.06–0.5	
	Ofloxacin	0.25	0.50	0.25–1.0	100
Staphylococcus aureus, penicillin resistant, methicillin susceptible (20)	Ciprofloxacin	0.25	1.0	0.12–4.0	90
	Levofloxacin	0.12	0.5	0.12–2.0	
	Ofloxacin	0.25	0.5	0.12–4.0	95
Staphylococcus aureus, methicillin resistant (17)	Ciprofloxacin	16.0	>64.0	0.5–>64	23
	Levofloxacin	8.0	16.0	0.25–32.0	
	Ofloxacin	16.0	32.0	0.50–64.0	18
Staphylococcus epidermidis, methicillin susceptible (11)	Ciprofloxacin	0.25	0.25	0.12–64.0	91
	Levofloxacin	0.12	0.25	0.12–8.0	
	Ofloxacin	0.25	0.50	0.12–16.0	91
Staphylococcus epidermidis, methicillin resistant (9)	Ciprofloxacin			4.0–64.0	0
	Levofloxacin			4.0–16.0	
	Ofloxacin			4.0–16.0	0
Staphylococcus hominis (15)	Ciprofloxacin	0.25	4.0	0.12–8.0	80
	Levofloxacin	0.25	4.0	0.12–8.0	
	Ofloxacin	0.25	4.0	0.12–8.0	86
Staphylococcus haemolyticus (14)	Ciprofloxacin	32.0	64.0	0.12–64.0	46
	Levofloxacin	16.0	32.0	0.12–32	
	Ofloxacin	32.0	64.0	0.12–64	46
Streptococcus pyogenes (10)	Ciprofloxacin	0.50	2.0	0.25–2.0	80
	Levofloxacin	0.50	2.0	0.25–2.0	
	Ofloxacin	1.0	4.0	0.50–4.0	80
Streptococcus agalactiae (20)	Ciprofloxacin	1.0	1.0	1.0–2.0	90
	Levofloxacin	1.0	2.0	1.0–2.0	
	Ofloxacin	2.0	4.0	1.0–4.0	85
Streptococcus group G (15)	Ciprofloxacin	0.50	0.50	0.25–0.50	100
	Levofloxacin	0.50	0.50	0.25–1.0	
	Ofloxacin	0.50	1.0	0.50–2.0	100
Streptococcus pneumoniae (20)	Ciprofloxacin	2.0	4.0	1.0–4.0	40
	Levofloxacin	1.0	2.0	0.5–2.0	
	Ofloxacin	2.0	4.0	1.0–4.0	55
Alpha-hemolytic viridans group streptococci (25)	Ciprofloxacin	2.0	8.0	≤0.03–>64.0	48
	Levofloxacin	1.0	2.0	≤0.03–4.0	
	Ofloxacin	2.0	4.0	≤0.03–8.0	72
Enterococcus faecalis (10)	Ciprofloxacin	1.0	2.0	0.5–2.0	80
	Levofloxacin	1.0	1.0	1.0–2.0	
	Ofloxacin	2.0	2.0	2.0–4.0	90
Enterococcus faecium (10)	Ciprofloxacin	1.0	2.0	0.5–4.0	60
	Levofloxacin	2.0	2.0	1.0–4.0	
	Ofloxacin	2.0	4.0	2.0–16.0	50
Bacillus spp. (15)	Ciprofloxacin	0.06	0.25	≤0.03–32	93
	Levofloxacin	0.12	0.25	0.06–64	
	Ofloxacin	0.25	0.50	0.12–8.0	93
Corynebacterium jeikeium (10)	Ciprofloxacin	32.0	>64.0	≤0.03–>64	30
	Levofloxacin	16.0	>64.0	0.12–>64	
	Ofloxacin	32.0	>64.0	0.25–>64	40
Listeria monocytogenes (10)	Ciprofloxacin	1.0	8.0	0.50–8.0	70
	Levofloxacin	2.0	8.0	1.0–8.0	
	Ofloxacin	2.0	8.0	1.0–8.0	50

[a] 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.

[b] Breakpoints used to determine the percentage of susceptible isolates were 1.0 μg/ml for ciprofloxacin and 2.0 μg/ml for ofloxacin. Susceptibility breakpoints for levofloxacin have not yet been accepted by the National Committee for Clinical Laboratory Standards.

and *Pseudomonas aeruginosa* (4). Levofloxacin has also been demonstrated to act synergistically when combined with oxacillin against quinolone- and oxacillin-resistant strains of *Staphylococcus aureus* (9). In addition to its recognized toxicity profile, ciprofloxacin has recently been shown to be associated, albeit infrequently, with the development of acute renal failure (7). If in addition to the potential advantages associated with levofloxacin it is also demonstrated to have a favorable toxicologic profile, it will be of considerable interest to clinicians in multiple situations, including the therapy of infections in patients with cancer.

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