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Antibacterial Activities of Ciprofloxacin, Norfloxacin, Oxolinic Acid, Cinoxacin, and Nalidixic Acid

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In vitro studies were performed comparing ciprofloxacin (Bay o 9867) and norfloxacin with three related organic acids. Ciprofloxacin was two to eight times more active than norfloxacin against 658 bacterial isolates representing 30 species. For all species tested, ciprofloxacin MICs for 90% inhibition were ≤ 2.0 μg/ml. Additional tests with 5,994 isolates detected only 37 (0.6%) strains resistant to 2.0 μg of ciprofloxacin per ml and 106 (1.8%) resistant to 1.0 μg/ml. Only 6 (0.1%) of the 5,994 strains were resistant to 16 μg of norfloxacin per ml, and 129 (2.1%) were resistant to 4.0 μg/ml. The majority of resistant strains were streptococci or *Pseudomonas* spp. Resistance among the *Enterobacteriaceae* was extremely rare (i.e., > 99.8% susceptible to both drugs).

Ciprofloxacin (Bay o 9867) is a new quinolone carboxylic acid derivative that is being developed for oral and parenteral use in treatment of systemic infections as well as urinary tract infections (1, 3, 5, 7, 9). Structurally, ciprofloxacin closely resembles norfloxacin, except that ciprofloxacin has a cyclopropyl group in the 1 position, whereas norfloxacin has an ethyl group in that position. In this report, we compare the in vitro activity of ciprofloxacin with that of norfloxacin and three related organic acids currently being used for treatment of urinary tract infections. Broth microdilution tests were first performed with 658 isolates representative of common bacterial species. To further document the incidence of resistance among isolates currently being encountered, all isolates selected for susceptibility testing in four different clinical laboratories were tested against ciprofloxacin and norfloxacin for 30 to 45 days.

MATERIALS AND METHODS

Antimicrobial agents. Ciprofloxin was supplied as laboratory standard powder by Miles Pharmaceuticals (West Haven, Conn.). Norfloxacin was provided by Merck Institute for Therapeutic Research, Rahway, N.J. Nalidixic acid was obtained from Sterling Winthrop Research Institute, Rensselaer, N.Y. Eli Lilly Research Laboratories, Indianapolis, Ind., provided cinoxacin and oxolinic acid. Ciprofloxacin was dissolved and diluted in sterile water, and the other drugs were dissolved in 0.1 N NaOH and diluted in sterile water.

Bacterial isolates. The 658 aerobic or facultatively anaerobic bacterial isolates used in the first phase of this study were collected from six geographically separate medical centers, and additional isolates were contributed by the Centers for Disease Control, Atlanta, Ga. The contributing laboratories include The Cleveland Clinic Foundation, Cleveland, Ohio; Northwestern Memorial Hospital, Chicago, Ill.; University of California at Davis Medical Center, Sacramento, Calif.; St. Francis Hospital, Wichita, Kans.; Kaiser-Permanente Regional Laboratory, Clackamas, Oreg.; St. Vincent Hospital and Medical Center, Portland, Oreg. Species represented in this collection are listed in Tables 1 and 2.

To further evaluate the incidence of resistance among clinical isolates currently being encountered, all isolates selected for susceptibility testing in the laboratories directed by four of the authors (L. W. Ayers, E. H. Gerlach, R. N. Jones, and H. M. Sommers) were tested against ciprofloxacin and norfloxacin for 30 to 45 days, or until at least 1,500 isolates were evaluated in each institution. One of the four contributors used an agar dilution testing system; the others used broth microdilution systems (6).

Susceptibility tests. Broth microdilution tests were performed as outlined by the National Committee for Clinical Laboratory Standards (6). The drugs were diluted in cation-supplemented Mueller-Hinton broth, and microdilution trays were stored at −20°C or colder. The inoculum was approximately 5×10^5 CFU/ml. For testing fastidious strains, 3% lysed horse blood was added to each well, and nicotinamide dinucleotide was also added (25 μg/ml) for testing *Haemophilus influenzae*. Agar dilution tests, using proteose peptone no. 3 supplemented with 1% hemoglobin and 1% Kellogg supplement, were performed for evaluating the susceptibility of *Neisseria gonorrhoeae*.

RESULTS

Table 1 summarizes the results of microdilution tests with 315 gram-negative bacilli. Ciprofloxacin was generally four to eight times more active than norfloxacin against the gram-negative bacilli. For all *Enterobacteriaceae*, *Acinetobacter* spp., and *Pseudomonas aeruginosa*, ciprofloxacin MICs for 90% inhibition (MIC_{90}s) were ≤1.0 μg/ml, and norfloxacin MIC_{90}s were ≤4.0 μg/ml. Supplemental data were later obtained with 16 *Salmonella* spp. and 20 *Shigella* spp. against ciprofloxacin but not with the comparative drugs (data not shown). For the *Shigella* spp., ciprofloxacin MICs ranged from 0.0008 to 0.03 μg/ml (MIC_{50}, 0.008 μg/ml; MIC_{90}, 0.015 μg/ml). With the *Salmonella* spp., ciprofloxacin MICs ranged from 0.004 to 0.03 μg/ml (MIC_{50}, 0.015 μg/ml; MIC_{90}, 0.03 μg/ml).

Table 2 summarizes in vitro data with other species that were tested. Ciprofloxacin, norfloxacin, and oxolinic acid were all effective against *Staphylococcus* spp., including 30

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TABLE 1. In vitro activity of ciprofloxacin and norfloxacin, compared with those of three organic acids, against gram-negative bacilli

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		Range	50%	90%
Escherichia coli (25)	Ciprofloxacin	0.008–0.03	0.015	0.015
	Norfloxacin	≤0.06–0.25	≤0.06	0.12
	Oxolinic acid	≤0.06–4.0	2.0	4.0
	Cinoxacin	1.0–4.0	2.0	4.0
	Nalidixic acid	0.5–8.0	2.0	4.0
Citrobacter spp. (20)[a]	Ciprofloxacin	0.004–0.12	0.008	0.03
	Norfloxacin	≤0.06–1.0	≤0.06	0.25
	Oxolinic acid	0.12–>32	0.25	0.5
	Cinoxacin	2.0–>128	2.0	4.0
	Nalidixic acid	2.0–>128	2.0	4.0
Enterobacter spp. (50)[b]	Ciprofloxacin	0.008–1.0	0.015	0.06
	Norfloxacin	≤0.06–8.0	0.12	0.25
	Oxolinic acid	0.12–16	0.25	0.5
	Cinoxacin	1.0–64	4.0	8.0
	Nalidixic acid	1.0–128	2.0	4.0
Klebsiella pneumoniae (24)	Ciprofloxacin	0.015–0.5	0.03	0.25
	Norfloxacin	0.12–2.0	0.12	0.25
	Oxolinic acid	0.25–4.0	0.25	0.5
	Cinoxacin	2.0–16	4.0	4.0
	Nalidixic acid	2.0–32	2.0	4.0
Serratia marcescens (25)	Ciprofloxacin	0.015–0.5	0.06	0.12
	Norfloxacin	≤0.06–2.0	0.12	0.5
	Oxolinic acid	0.12–2.0	0.25	0.25
	Cinoxacin	2.0–64	4.0	16
	Nalidixic acid	0.5–16	1.0	4.0
Proteus mirabilis (25)	Ciprofloxacin	0.015–0.06	0.015	0.03
	Norfloxacin	≤0.06–0.25	≤0.06	0.12
	Oxolinic acid	0.12–0.5	0.12	0.25
	Cinoxacin	2.0–8.0	4.0	4.0
	Nalidixic acid	1.0–8.0	2.0	4.0
Proteus vulgaris (10)	Ciprofloxacin	0.008–0.12	0.015	0.06
	Norfloxacin	≤0.06–0.25	≤0.06	0.12
	Oxolinic acid	0.12–0.5	0.12	0.25
	Cinoxacin	2.0–8.0	4.0	4.0
	Nalidixic acid	1.0–8.0	2.0	4.0
Morganella morganii (10)	Ciprofloxacin	0.008–0.06	0.015	0.015
	Norfloxacin	0.12–2.0	0.12	0.25
	Oxolinic acid	0.25–4.0	0.25	0.5
	Cinoxacin	2.0–16	4.0	4.0
	Nalidixic acid	2.0–32	2.0	4.0
Providencia rettgeri (10)	Ciprofloxacin	0.015–8.0	0.03	1.0
	Norfloxacin	≤0.06–>32	0.25	4.0
	Oxolinic acid	≤0.06–8.0	0.5	4.0
	Cinoxacin	1.0–>128	4.0	>128
	Nalidixic acid	1.0–>128	4.0	128
Providencia stuartii (20)	Ciprofloxacin	0.008–2.0	0.03	0.5
	Norfloxacin	≤0.06–16	0.12	2.0
	Oxolinic acid	0.12–4.0	0.25	4.0
	Cinoxacin	1.0>128	4.0	>128
	Nalidixic acid	1.0–>128	4.0	64
Acinetobacter calcoaceticus subsp. *antitratus* (15)	Ciprofloxacin	0.12–0.5	0.25	0.5
	Norfloxacin	1.0–4.0	2.0	4.0
	Oxolinic acid	0.12–1.0	0.25	1.0
	Cinoxacin	16–64	64	64
	Nalidixic acid	1.0–8.0	4.0	4.0
Pseudomonas aeruginosa (50)	Ciprofloxacin	0.03–1.0	0.25	1.0
	Norfloxacin	0.12–4.0	0.5	2.0
	Oxolinic acid	1.0–>32	8.0	32
	Cinoxacin	8.0–>128	>128	>128
	Nalidixic acid	8.0–>128	64	>128
Other *Pseudomonas* species (31)[c]	Ciprofloxacin	0.004–8.0	0.12	2.0
	Norfloxacin	≤0.06–32	0.25	16
	Oxolinic acid	0.12–8.0	0.5	4.0
	Cinoxacin	1.0–>128	16	>128
	Nalidixic acid	0.5–64	8.0	32

[a] Includes 10 *C. diversus* and 10 *C. freundii isolates.*

[b] Includes 20 *E. aerogenes*, 10 *E. agglomerans*, and 20 *E. cloacae* isolates.

[c] Includes 10 *P. stutzeri*, 6 *P. cepacia*, 5 *P. fluorescens*, 5 *P. putida*, 3 *P. maltophila*, and 2 *P. acidovorans* isolates.

isolates of methicillin-resistant *S. aureus*. Norfloxacin was two to four times more active than oxolinic acid, and ciprofloxacin was two to four times more active than norfloxacin.

The streptococci were relatively resistant to all five drugs; ciprofloxacin was the most active compound, with MIC_{50}s of approximately 1.0 μg/ml. *H. influenzae* and the two *Neisseria* species were extremely susceptible to ciprofloxacin (MIC_{90}s ≤ 0.008 μg/ml). Norfloxacin and oxolinic acid also had in vitro activity against *H. influenzae* and the meningococci.

Our current culture collection contains very few strains that were resistant to any of the quinolone derivatives. Additional data were collected to determine the incidence of resistance to ciprofloxacin and norfloxacin among a large sample of current clinical isolates. Four geographically separate medical centers performed dilution tests with all isolates that were selected for susceptibility testing over a 30- to 45-day period or until each laboratory tested at least 1,500 isolates. Quality control tests documented no methodological differences among laboratories. When data from each institution were tabulated separately, comparing data with those species that were represented by enough strains to warrant comparison, MIC_{50}s and MIC_{90}s were essentially the same (±1 $\log_2$ dilution). There was no trend for the data from the laboratory using agar dilution tests to differ from those generated by broth dilution tests. Consequently, the data were combined for presentation in this report.

Table 3 shows the results of such tests for those species that were represented by at least 15 isolates. Tentative MIC breakpoints for systemic therapy with ciprofloxacin were ≤1.0 μg/ml for susceptible isolates and >2.0 μg/ml for resistant isolates. For treating urinary tract infections with norfloxacin, higher breakpoints have been recommended (i.e., ≤16 μg/ml for the susceptible category and >16 μg/ml for the resistant category [8]). For the disk test, the susceptible breakpoint actually correlates with an MIC of ≤4.0 μg/ml: strains requiring MICs of 8.0 or 16 μg/ml may be considered moderately susceptible or intermediate in susceptibility to norfloxacin (8). The percentages of strains inhibited at these breakpoint concentrations are listed in Table 3. Among the 4,039 *Enterobacteriaceae*, all but five strains were inhibited by 1.0 μg of ciprofloxacin per ml and all but eight strains were inhibited by 4.0 μg of norfloxacin per ml. Only one isolate (*Enterobacter aerogenes*) was

TABLE 2. In vitro activity of ciprofloxacin and norfloxacin, compared with those of three organic acids, against gram-positive cocci, *Haemophilus* and *Neisseria* species

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		Range	50%	90%
Staphylococcus aureus (methicillin susceptible) (50)[a]	Ciprofloxacin	0.12–0.5	0.25	0.5
	Norfloxacin	0.25–4.0	1.0	2.0
	Oxolinic acid	1.0–4.0	2.0	2.0
	Cinoxacin	16–>128	64	128
	Nalidixic acid	16–128	64	128
Staphylococcus aureus (methicillin resistant) (30)	Ciprofloxacin	0.12–0.5	0.25	0.5
	Norfloxacin	0.5–1.0	0.5	1.0
	Oxolinic acid	1.0–2.0	2.0	2.0
	Cinoxacin	32–128	64	128
	Nalidixic acid	16–64	32	64
Staphylococcus spp. (coagulase negative) (25)[b]	Ciprofloxacin	0.06–0.5	0.25	0.5
	Norfloxacin	0.25–2.0	0.5	1.0
	Oxolinic acid	1.0–16	4.0	8.0
	Cinoxacin	32–>128	128	>128
	Nalidixic acid	16–>128	64	128
Streptococcus faecalis (26)	Ciprofloxacin	0.5–2.0	1.0	2.0
	Norfloxacin	1.0–8.0	4.0	4.0
	Oxolinic acid	16–>32	32	32
	Cinoxacin	128–>128	>128	>128
	Nalidixic acid	>128–>128	>128	>128
Streptococcus pyogenes (20)	Ciprofloxacin	0.5–2.0	0.5	2.0
	Norfloxacin	1.0–32	2.0	32
	Oxolinic acid	>32–>32	>32	>32
	Cinoxacin	>128–>128	>128	>128
	Nalidixic acid	>128–>128	>128	>128
Streptococcus agalactiae (20)	Ciprofloxacin	0.5–1.0	1.0	1.0
	Norfloxacin	4.0–8.0	4.0	8.0
	Oxolinic acid	32–>32	>32	>32
	Cinoxacin	64–>128	>128	>128
	Nalidixic acid	64–>128	>128	>128
Streptococcus pneumoniae (20)[c]	Ciprofloxacin	0.5–4.0	1.0	2.0
	Norfloxacin	4.0–32	4.0	16
	Oxolinic acid	>32–>32	>32	>32
	Cinoxacin	>128–>128	>128	>128
	Nalidixic acid	>128–>128	>128	>128
Haemophilus influenzae (40)[d]	Ciprofloxacin	0.004–0.015	0.008	0.008
	Norfloxacin	≤0.06–≤0.06	≤0.06	≤0.06
	Oxolinic acid	≤0.06–≤0.06	≤0.06	≤0.06
	Cinoxacin	0.5–1.0	1.0	1.0
	Nalidixic acid	≤0.25–1.0	0.5	0.5
Neisseria meningitidis (26)	Ciprofloxacin	≤0.0005–0.004	0.004	0.004
	Norfloxacin	≤0.06–≤0.06	≤0.06	≤0.06
	Oxolinic acid	≤0.12–0.25	≤0.12	≤0.12
	Cinoxacin	0.25–2.0	0.5	2.0
	Nalidixic acid	≤0.12–1.0	0.25	0.5
Neisseria gonorrhoeae (50)[e]	Ciprofloxacin	≤0.0005–0.008	0.002	0.008
	Norfloxacin	≤0.06–≤0.06	≤0.06	≤0.06

[a] Includes 26 penicillin-resistant strains.
[b] Includes 19 penicillin-resistant strains.
[c] Includes 11 strains that were relatively resistant to benzyl penicillin (MIC > 0.06 μg/ml).
[d] Includes 20 beta-lactamase-positive strains.
[e] Includes 25 beta-lactamase-positive strains; only two drugs were tested.

resistant to norfloxacin (MIC > 16 μg/ml). Three *Enterobacteriaceae* (one *Escherichia coli*, one *Klebsiella pneumoniae*, and one *Serratia marcescens*) were resistant to ciprofloxacin (MIC = 4.0 μg/ml for all three). All 31 isolates of *Acinetobacter calcoaceticus* were inhibited by 1.0 μg of ciprofloxacin or 16 μg of norfloxacin per ml; only 87.1% were susceptible to 4.0 μg of norfloxacin per ml. Among the 577 *P. aeruginosa* isolates, 7 were resistant to ciprofloxacin

TABLE 3. Susceptibility to ciprofloxacin and norfloxacin among all common bacterial pathogens submitted for susceptibility testing in four medical centers during a 30- to 45-day period

Microorganism (no. of isolates)	% Inhibited by the following concn (μg/ml) of:			
	Ciprofloxacin		Norfloxacin	
	≤1.0	≤2.0	≤4.0	≤16
Escherichia coli (2,204)	99.7	99.9	99.7	100
Citrobacter				
diversus (49)	100	100	100	100
freundii (70)	100	100	100	100
Enterobacter				
aerogenes (166)	100	100	99.4	99.4
agglomerans (19)	100	100	100	100
cloacae (211)	100	100	100	100
Klebsiella				
oxytoca (103)	100	100	100	100
pneumoniae (509)	99.6	99.8	100	100
Serratia marcescens (122)	99.2	99.2	99.2	100
Proteus				
mirabilis (384)	99.7	100	100	100
vulgaris (30)	100	100	100	100
Morganella morganii (99)	100	100	100	100
Providencia stuartii (58)	100	100	100	100
Salmonella enteritidis (15)	100	100	100	100
Acinetobacter calcoaceticus (31)	100	100	87.1	100
Pseudomonas				
aeruginosa (577)	97.7	98.8	96.9	99.5
maltophilia (20)	60.0	70.0	30.0	95.0
Staphylococcus				
aureus (464)	99.8	100	99.6	100
Other species (359)	99.4	99.4	99.4	100
Streptococcus				
faecalis (474)	87.8	98.7	87.1	100
faecium-durans (30)	50.0	60.0	30.0	96.7

(MIC > 2.0 μg/ml) and three were resistant to norfloxacin (MIC > 16 μg/ml). An additional 6 *P. aeruginosa* isolates required intermediate ciprofloxacin MICs, and 15 required intermediate norfloxacin MICs. Among the staphylococci, >99% were susceptible to both drugs. Approximately 87% of the *Streptococcus faecalis* isolates were susceptible to both drugs; all strains were susceptible to norfloxacin at 16 μg/ml. *Streptococcus faecium* and *Streptococcus durans* tended to be more resistant than *S. faecalis*.

Among the 5,994 isolates listed in Table 3, only 37 (0.6%) isolates were resistant to ciprofloxacin (MIC ≥ 4.0 μg/ml), and 69 (1.1%) were intermediate in susceptibility (MIC, 2.0 μg/ml). Only six isolates (0.1%) were resistant to norfloxacin (MIC ≥ 32 μg/ml), and an additional 123 (2.0%) isolates required intermediate MICs of 8.0 or 16 μg/ml.

DISCUSSION

Ciprofloxacin, like other related compounds in the "organic acid" category of antimicrobial agents, has a very broad spectrum of activity. Similarities in the spectra of activity have been noted by others (3, 4, 8) and are confirmed by the data in this report. Ciprofloxacin differs from norfloxacin primarily by the fact that ciprofloxacin is approximately four times more active than norfloxacin. In the same way, norfloxacin is more active than oxolinic acid which, in turn, is more potent than cinoxacin or nalidixic acid. Norfloxacin and the earlier organic acids are limited to treatment of urinary tract infections because effective blood levels cannot be achieved safely. Because of the increased potency of ciprofloxacin, it may be useful for treating systemic infections as well as urinary tract infections.

No serious side effects or remarkably adverse reactions were observed when ciprofloxacin was administered to human volunteers, either intravenously (W. Wingender, K.-H. Graefe, W. Gav, D. Foerster, R. Ziegler, P. Schacht, and U. Lietz, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 852, 1983) or orally (R. Ziegler, K.-H. Graefe, W. Wingender, W. Gav, H.-J. Zeiler, U. Lietz, and P. Schacht, 23rd ICAAC, abstr. no. 851). In both of these studies, serum levels exceeded 1.0 μg/ml. Crump et al. (2) reported pharmacokinetic studies after administration of a single 500-mg tablet. Peak serum levels of 2.4 μg/ml were achieved 1.25 h after administration, and the serum half-life was estimated to be 3.9 h. Approximately 57% of the drug in the serum penetrated into blister fluid. Approximately 30% of the drug was excreted in the urine within 24 h after dosing.

These pharmacokinetic studies form the basis for assuming that strains requiring MICs ≤ 1.0 μg/ml should be considered susceptible and those requiring MICs ≥ 4.0 μg/ml should be considered resistant. The majority of isolates with intermediate susceptibility (MIC, 2.0 μg/ml) are streptococci. In our series of 474 *S. faecalis* isolates, 87.8% were inhibited by 1.0 μg/ml and 98.7% were inhibited by 2.0 μg/ml. In our studies, the *Enterobacteriaceae* (Table 1) were significantly more susceptible than were the common *Streptococcus* species (Table 2). Similar findings have been reported by other authors (1, 3, 5, 7). The staphylococci generally require 0.25 to 0.5 μg/ml for inhibition. Methicillin-resistant strains of *S. aureus* were just as susceptible to ciprofloxacin as methicillin-susceptible strains (Table 2).

By twice-daily dosing with 500-mg tablets, serum levels in excess of 1.0 μg/ml can be achieved, and that is well above the MIC_{90} for all of the common bacterial pathogens, except for the streptococci. For that reason, ciprofloxacin appears to be a valuable therapeutic agent for treating many systemic infections as well as urinary tract infections. Its efficacy in treating streptococcal or staphylococcal infections remains to be seen. In treating infections caused by the *Enterobacteriaceae*, clinical efficacy should be anticipated, especially when treating urinary tract infections.

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