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Multicenter Evaluation of the In Vitro Activities of Three New Quinolones, Sparfloxacin, CI-960, and PD 131,628, Compared with the Activity of Ciprofloxacin against 5,252 Clinical Bacterial Isolates

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The in vitro activities of three new quinolones (sparfloxacin, CI-960, and PD 131,628) were compared with that of ciprofloxacin against 5,252 routine clinical aerobic and facultatively anaerobic bacterial isolates. Overall, CI-960 was the most active drug in vitro (MIC for 90% of the strains tested, 0.13 μg/ml); ciprofloxacin and sparfloxacin were the least active (MIC for 90% of the strains tested, 1.0 μg/ml). All three new quinolones, but particularly CI-960 and PD 131,628, exhibited significantly greater activity than ciprofloxacin against enterococci and staphylococci.

The recent resurgence of clinical use of quinolones in the treatment of bacterial infections is due to the development of the new fluorinated compounds which exhibit both greater potency and broader spectra of antibacterial activity. Despite this increased activity, resistance to currently available drugs, such as ciprofloxacin, is not uncommon among some species of gram-positive cocci, particularly enterococci and some staphylococci. Thus, the search for more effective compounds continues.

The purpose of this report is to describe the comparative in vitro activities of three new fluorinated quinolones versus that of ciprofloxacin against 5,252 routine clinical bacterial isolates at four major medical centers. Sparfloxacin (AT-4140, CI-978, or PD 131,501) has been reported to have in vitro antibacterial activity comparable to that of ciprofloxacin but was less active against *Pseudomonas aeruginosa* and more active against enterococci and staphylococci (2, 4, 5). CI-960 (AM-1091 or PD 127,391) has also been reported to be more active than ciprofloxacin against gram-positive cocci (3, 7). The in vitro activity of PD 131,628 has been described by Cohen et al. (1).

The three test drugs, sparfloxacin, CI-960, and PD 131,628, were provided as standardized powders by Warner-Lambert Co., Ann Arbor, Mich. Ciprofloxacin was obtained from Miles Pharmaceuticals, West Haven, Conn. Participating laboratories included the clinical microbiology laborato-

TABLE 1. Distribution of MIC endpoints of four quinolones with four standard quality control organisms[a]

Control strain	Antimicrobial agent	No. of times each of the following MICs (μg/ml) was recorded[b]:								
		≤0.016	0.03	0.06	0.13	0.25	0.5	1.0	2.0	>2.0
Enterococcus faecalis ATCC 29212	Ciprofloxacin					[2	58	16	0]	
	Sparfloxacin					49	26			
	CI-960			50	26					
	PD 131,628				57	19				
Staphylococcus aureus ATCC 29213	Ciprofloxacin				[2	57	18]			
	Sparfloxacin			63	13					
	CI-960	35	42							
	PD 131,628			70	7					
Escherichia coli ATCC 25922	Ciprofloxacin	[76]	1	1						
	Sparfloxacin	64	14							
	CI-960	76	2							
	PD 131,628	76	2							
Pseudomonas aeruginosa ATCC 27853	Ciprofloxacin					[16	61	1]		
	Sparfloxacin							59	18	1
	CI-960				57	21				
	PD 131,628				51	27				

[a] See reference 6.
[b] Brackets enclose currently recommended control limits for tests with ciprofloxacin (6).

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TABLE 2. MIC_{90}s and MIC ranges of four quinolones against 5,252 routine clinical bacterial isolates

Organism(s) (no.of isolates)	MIC (μg/ml)							
	Sparfloxacin		CI-960		PD 131,628		Ciprofloxacin	
	90%	Range	90%	Range	90%	Range	90%	Range
Citrobacter diversus (42)	0.06	≤0.016–1.0	≤0.016	≤0.016–0.13	≤0.016	≤0.016–0.13	0.03	≤0.016–0.25
C. freundii (84)	1.0	≤0.016–>2.0	0.13	≤0.016–>2.0	0.13	≤0.016–>2.0	0.13	≤0.016–>2.0
C. amalonaticus (14)	0.25	0.03–0.25	0.03	≤0.016–0.03	0.03	≤0.016–0.3	0.06	≤0.016–0.13
Enterobacter aerogenes (118)	0.13	≤0.016–0.5	0.03	≤0.016–0.13	0.03	≤0.016–0.13	0.06	≤0.016–0.25
E. agglomerans (16)	0.13	≤0.016–0.25	0.03	≤0.016–0.06	0.06	≤0.016–0.06	0.06	≤0.016–0.25
E. cloacae (244)	0.13	≤0.016–2.0	0.03	≤0.016–0.5	0.03	≤0.016–1.0	0.06	≤0.016–>2.0
E. sakazakii (11)	0.06	0.03–0.06	≤0.016	≤0.016–0.03	≤0.016	≥0.016	0.03	≤0.016–0.03
Enterobacter sp. (NOS)[a] (11)	1.0	0.03–2.0	0.25	≤0.016–1.0	0.5	≤0.016–1.0	2.0	≤0.016–2.0
Escherichia coli (1256)	0.03	≤0.016–2.0	≤0.016	≤0.016–0.25	≤0.016	≤0.016–0.5	0.03	≤0.016–0.06
Klebsiella oxytoca (111)	0.13	≤0.016–0.5	≤0.016	≤0.016–0.13	≤0.016	≤0.016–0.13	0.06	≤0.016–0.25
K. pneumoniae (312)	0.25	≤0.016–>2.0	0.06	≤0.016–>2.0	0.06	≤0.016–>2.0	0.25	≤0.016–>2.0
Morganella morganii (39)	0.5	0.03–>2.0	0.06	≤0.016–1.0	0.06	≤0.016–>2.0	0.06	≤0.016–>2.0
Proteus mirabilis (200)	0.5	≤0.016–1.0	0.03	≤0.016–0.25	0.06	≤0.016–0.5	0.06	≤0.016–2.0
P. vulgaris (12)	0.5	0.06–0.5	0.03	≤0.016–0.03	0.03	≤0.016–0.06	0.06	≤0.016–0.06
Providencia rettgeri (11)	2.0	0.06–>2.0	0.25	≤0.016–0.5	0.5	≤0.016–0.5	1.0	≤0.016–>2.0
Serratia liquefaciens (10)	0.13	0.03–0.13	≤0.016	≤0.016	0.03	≤0.016–0.03	0.03	≤0.016–0.03
S. marcescens (96)	2.0	0.03–>2.0	0.25	≤0.016–2.0	0.5	≤0.016–2.0	0.5	≤0.016–>2.0
Other enteric bacteria[b] (14)	0.13	≤0.016–0.13	0.03	≤0.016–0.03	0.03	≤0.016–0.03	0.03	≤0.016–0.06
All members of the family *Enterobacteriaceae* (2,601)	0.25	≤0.016–>2.0	0.03	≤0.016–>2.0	0.03	≤0.016–>2.0	0.06	≤0.016–>2.0
Acinetobacter anitratus (49)	0.25	≤0.016–1.0	0.13	≤0.016–1.0	0.25	≤0.016–2.0	1.0	0.06–>2.0
Pseudomonas aeruginosa (365)	>2.0	0.03–>2.0	1.0	<0.016–>2.0	1.0	≤0.016–>2.0	1.0	≤0.016–>2.0
P. fluorescens-P. putida (10)	>2.0	0.25–>2.0	2.0	0.03–2.0	1.0	0.03–2.0	>2.0	≤0.06–>2.0
Xanthomonas maltophilia (57)	>2.0	0.03–>2.0	2.0	≤0.016–>2.0	>2.0	≤0.016–>2.0	>2.0	0.06–>2.0
Other nonenteric gram-negative bacteria[c] (23)	2.0	≤0.016–>2.0	0.5	≤0.016–>2.0	1.0	≤0.016–>2.0	>2.0	≤0.016–>2.0
Enterococcus faecalis (198)	1.0	0.13–>2.0	0.25	0.03–>2.0	0.5	0.13–>2.0	2.0	0.25–>2.0
E. faecium (33)	1.0	0.5–2.0	0.5	0.13–1.0	1.0	0.25–2.0	>2.0	0.5–2.0
Enterococcus sp. (NOS) (197)	1.0	0.13–>2.0	0.5	≤0.016–>2.0	1.0	0.06–>2.0	2.0	0.13–>2.0
Streptococcus agalactiae (79)	0.5	0.13–1.0	0.13	0.03–0.13	0.5	0.13–1.0	1.0	0.5–2.0
Staphylococcus aureus (984)	0.13	≤0.016–>2.0	0.06	≤0.016–>2.0	0.13	≤0.016–>2.0	1.0	≤0.016–>2.0
S. epidermidis (260)	>2.0	≤0.016–>2.0	0.25	≤0.016–1.0	2.0	≤0.016–>2.0	>2.0	≤0.016–>2.0
S. haemolyticus (26)	>2.0	0.06–>2.0	1.0	≤0.016–1.0	>2.0	0.03–>2.0	>2.0	0.13–>2.0
S. hominis (15)	0.5	0.06–>2.0	0.06	≤0.016–1.0	0.13	≤0.016–>2.0	0.5	0.13–>2.0
S. simulans (14)	0.13	0.03–0.25	0.06	≤0.016–0.06	0.13	≤0.016–0.13	0.5	0.13–0.5
S. saprophyticus (11)	0.25	0.13–0.25	0.13	0.06–0.13	0.13	0.06–0.25	0.5	0.5–1.0
Staphylococcus spp. (CN)[d] (330)	>2.0	≤0.016–>2.0	0.25	≤0.016–2.0	>2.0	≤0.016–>2.0	>2.0	≤0.016–>2.0
All organisms (5,252)	1.0		0.13		0.5		1.0	

[a] NOS, No other specification.
[b] Includes six *Hafnia alvei* and eight *Salmonella enteritidis* isolates.
[c] Includes eight *Acinetobacter lwoffii*, six *Aeromonas* spp., and seven *Pseudomonas* spp. not specified above.
[d] CN, Coagulase-negative staphylococci not further identified.

ries of Indiana University Medical Center, Indianapolis; St. Francis Medical Center, Wichita, Kans.; St. Vincent Hospital and Medical Center, Portland, Oreg.; and University of Iowa Hospitals and Clinics, Iowa City. Each laboratory prepared its own microdilution susceptibility test trays, each of which contained twofold dilutions of each drug ranging from 2.0 to 0.0156 μg/ml. All laboratories tested consecutive routine clinical isolates of nonfastidious bacteria by routine susceptibility testing over a 30- to 45-day period. Procedures outlined by the National Committee for Clinical Laboratory Standards for microdilution susceptibility tests were followed by all participants (6). The MIC was defined as the lowest drug concentration preventing grossly visible bacterial growth. The four quality control organisms recommended by the National Committee for Clinical Laboratory Standards (6) were tested on each day of testing. The distribution of endpoints obtained by the four participating laboratories is summarized in Table 1. Of the ciprofloxacin endpoints, all but two MICs were within the acceptable ranges (6). For the three test quinolones, offscale endpoints (≤0.016 μg/ml) were seen with 4 of the 12 drug-organism pairings and 8 others varied over a range of 2 dilutions; one pairing had a range of 3 dilutions (Table 1).

Susceptibility data for these four quinolones determined with 5,252 bacterial isolates are summarized in Table 2. Members of the family *Enterobacteriaceae* were highly susceptible to all four drugs. Against this family of bacteria, CI-960 and PD 131,628 were most active, with an MIC for 90% of the organisms tested (MIC_{90}) of 0.03 μg/ml, compared with 0.06 and 0.25 μg/ml for ciprofloxacin and sparfloxacin, respectively. For all of the drugs, the highest MIC_{90}s occurred with *Serratia marcescens* and *Providencia rettgeri*, but only the MIC_{90} of sparfloxacin was >1.0 μg/ml.

All four quinolones showed good activity against nonen-

teric gram-negative bacilli, although it was substantially less than that against members of the family *Enterobacteriaceae*. Ciprofloxacin, CI-960, and PD 131,628 were comparably active against *Pseudomonas aeruginosa*, each having a MIC_{90} of 1.0 μg/ml. *Xanthomonas maltophilia* was the organism most resistant to all four drugs, but CI-960 had the lowest MIC_{90} (2.0 μg/ml). The MIC_{75}s for these species were ≥2.0 μg/ml for ciprofloxacin, 1.0 μg/ml for sparfloxacin and PD 131,628, and 0.5 μg/ml for CI-960. CI-960 was most active against *Acinetobacter anitratus* (MIC_{90}, 0.13 μg/ml), and ciprofloxacin was least active (MIC_{90}, 1.0 μg/ml). The relative activities of these four quinolones against nonenteric gram-negative bacilli as a group were as follows: CI-960 > PD 131,628 > ciprofloxacin > sparfloxacin.

Only two-thirds of enterococcal isolates were susceptible to ≤1.0 μg of ciprofloxacin per ml, the MIC_{90} for which was 2.0 μg/ml. Sparfloxacin and PD 131,628 exhibited comparable activities against enterococci and *Streptococcus agalactiae*, and their MIC_{90}s were half of those of ciprofloxacin. CI-960 was at least twice as active as the other quinolones against enterococci and *S. agalactiae*.

The staphylococci exhibited some species variability in their susceptibilities to these four compounds. Although *Staphylococcus aureus* was generally susceptible to ciprofloxacin (MIC_{90}, 1.0 μg/ml), the MIC_{90}s of the other three drugs were 8- to 16-fold lower. Whereas 66 (6.7%) of 984 *S. aureus* isolates were resistant (MIC, ≥4.0 μg/ml) to ciprofloxacin, 56 (5.7%) and 55 (5.6%) were resistant to sparfloxacin and PD 131,628, respectively, and only 1 (0.1%) required ≥4.0 μg of CI-960 per ml for inhibition. Sparfloxacin, ciprofloxacin, and PD 131,628 had MIC_{90}s of >2.0 μg/ml for *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*, and for *S. haemolyticus* the MIC_{50}s of these three drugs were also >2.0 μg/ml. But all isolates of these two species were susceptible to ≤1.0 μg of CI-960 per ml. Other staphylococcal species were susceptible to all four drugs, but ciprofloxacin MICs were generally higher than those of the other compounds.

These four quinolone compounds exhibit potent broad-spectrum antibacterial activities against routine clinical bacterial isolates which grow aerobically. The relative activities, expressed as MIC_{90}s for all 5,252 bacterial isolates combined, were as follows: CI-960 (MIC_{90}, 0.13 μg/ml) > PD 131,680 (MIC_{90}, 0.5 μg/ml) > sparfloxacin = ciprofloxacin (MIC_{90}s, 1.0 μg/ml). The percentages of the 5,252 isolates inhibited by 1.0 μg of drug per ml were 98.9, 95.7, 93.6, and 91.8%, respectively. Although the proportions of susceptible and resistant strains within some species (e.g., *S. aureus*) varied substantially between different institutions in the study, the relative activities of the four test drugs were the same in each institution. Because of their in vitro activities, these new quinolone agents merit further study.

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