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In Vitro and In Vivo Activities of Clinafloxacin, CI-990 (PD 131112), and PD 138312 versus Enterococci

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Certain new fluoroquinolones have high activity against enterococci. Against *Enterococcus faecalis* ($n = 18$), MICs at which 90% of the isolates were inhibited were as follows (in micrograms per milliliter): clinafloxacin, 0.125; CI-990, 0.5; and PD 138312, 0.25 (compared with 1 μg/ml for ciprofloxacin and 2 μg/ml for ofloxacin). Strains producing β-lactamase or that were vancomycin resistant or resistant to high-level gentamicin were not quinolone cross-resistant. The drugs were bactericidal and were unaffected by 50% human serum. Oral efficacies (in milligrams per kilogram of body weight for 50% protective doses) in lethal mouse infections with quinolone-susceptible strains were 4.3 to 24 for clinafloxacin, 7.2 to 39 for CI-990, 7.2 to 76 for PD 138312, and 41 to >100 for ciprofloxacin; when the drugs were given subcutaneously, the order was similar and values ranged from 1.1 to 12.5. Clinafloxacin, CI-990, and PD 138312 may have therapeutic potential in systemic enterococcal infections in humans.

Enterococci have gained increasing recognition as primary human pathogens. Resistance to penicillins, aminoglycosides, and glycopeptides (6, 13, 14, 20–22) and to quinolones such as ciprofloxacin (18) has emerged. Clinafloxacin (CI-960; PD 127391), CI-990 (PD 131112), and PD 138312 are new fluoroquinolones possessing high in vitro activities against enterococci (4, 5, 8); clinical trials are in progress in the United States for clinafloxacin and CI-990. This report documents in vitro and in vivo activities against antibiotic-resistant *Enterococcus* strains.

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The compounds used and their sources were as follows: clinafloxacin, CI-990 (PD 131112; the L-alanyl amide prodrug used for in vivo testing), PD 131628 (the parent form of CI-990 used for in vitro testing), PD 138312, and ofloxacin, Parke-Davis Pharmaceutical Research, Ann Arbor, Mich.; clavulanic acid, Beecham Laboratories, Bristol, Tenn.; imipenem, Merck Sharp & Dohme, West Point, Pa.; teicoplanin, Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio; ciprofloxacin, Miles Inc., Pharmaceutical Division, West Haven, Conn.; and ampicillin, amoxicillin, cefazolin, gentamicin, rifampin, and vancomycin, Sigma Chemical Co., St. Louis, Mo. Figure 1 presents diagrams of the chemical structures of the fluoroquinolones.

Most isolates were of clinical origin. Some representative resistant isolates were generously donated by M. J. Zervos, William Beaumont Hospital, Royal Oak, Mich.; J. M. Swenson, Centers for Disease Control, Atlanta, Ga.; D. B. Clewell, University of Michigan Dental School, Ann Arbor, Mich.; and C. A. Kauffman, Ann Arbor Veterans Administration Medical Center, Ann Arbor, Mich. The typical *Enterococcus faecalis* strain MGH-2 was obtained from B. A. Waisbiren, Milwaukee General Hospital, Milwaukee, Wis. The National Committee for Clinical Laboratory Standards-sanctioned (15) reference *E. faecalis* strain ATCC 29212 was from the American Type Culture Collection, Rockville, Md.

Determination of MICs and MBCs were according to National Committee for Clinical Laboratory Standards (15, 16). Susceptibility testing was performed with unenriched cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) incubated at 35°C.

Frequencies of single-step spontaneous mutations were determined in duplicate by spreading ~10^{11} CFU onto Mueller-Hinton agar (Difco Laboratories) containing drugs; colonies were counted after 24 to 72 h of incubation. Multistep resistance selection measured increases in MICs over daily transfers in 5-ml volumes (0.1-ml inoculum harvested from a tube

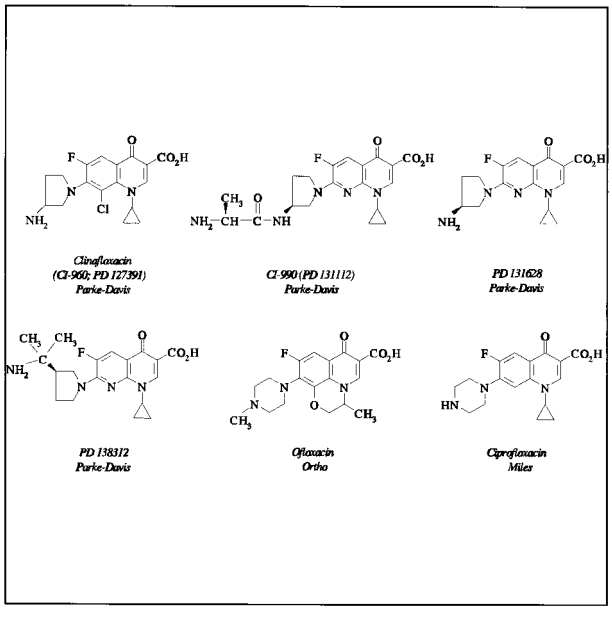

FIG. 1. Fluoroquinolone chemical structures.

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TABLE 1. In vitro activities versus enterococci for clinafloxacin, CI-990, PD 138312 and comparator antimicrobic agents

Organism (no. of strains)	Antimicrobial agent	MIC (μg/ml)[a]		
		Range	50%	90%
E. faecalis (17)	Clinafloxacin	0.06–0.125	0.06	0.125
	CI-990[b]	0.125–0.5	0.25	0.5
	PD 138312	0.06–0.25	0.125	0.25
	Ciprofloxacin	0.25–2	1	1
	Ofloxacin	1–4	2	2
	Imipenem	0.25–1	0.5	1
	Ampicillin	0.25–2	1	2
	Amox./clav.[c]	0.25/0.125–0.5/0.25	0.5/0.25	0.5/0.25
	Vancomycin	0.5–2	1	2
	Teicoplanin	0.125–0.25	0.125	0.25
	Rifampin	1–8	2	4
Ciprofloxacin-resistant *E. faecalis* (11)	Clinafloxacin	0.5–32	4	8
	CI-990	1–64	16	16
	PD 138312	0.5–128	4	32
	Ciprofloxacin	4–>128	64	64
E. faecium (10)	Clinafloxacin	0.125–8	0.5	0.5
	CI-990	0.25–32	2	2
	PD 138312	0.06–16	2	2
	Ciprofloxacin	0.5–>128	2	4
	Ofloxacin	2–>128	8	8
	Imipenem	0.5–128	32	128
	Ampicillin	0.5–64	8	64
	Amox./clav.	0.25/0.125–32/16	4/2	32/16
	Vancomycin	0.5–2	0.5	2
	Teicoplanin	0.25–1	0.5	0.5
	Rifampin	0.015–16	8	16
Vancomycin-resistant *E. faecium* (12)	Clinafloxacin	0.125–0.5	0.5	0.5
	CI-990	0.25–2	1	2
	PD 138312	0.25–4	2	2
	Ciprofloxacin	0.5–4	2	4
	Ofloxacin	2–8	4	8
	Imipenem	4–>128	64	128
	Ampicillin	4–128	64	128
	Amox./clav.	2/1–64/32	32/16	64/32
	Vancomycin	32–>128	>128	>128
	Teicoplanin	0.25–>128	32	>128
	Rifampin	0.008–16	8	8

[a] 50% and 90% refer to MIC_{50} and MIC_{90}, respectively.
[b] PD 131628 parent used for MIC testing.
[c] 2:1 ratio of amoxicillin to clavulanic acid.

from the previous passage corresponding to the highest concentration of drug permitting growth that was virtually equal to that of the drug-free control tube).

Acute lethal infection in 18- to 22-g CD-1 female mice (Charles River Laboratories, Portage, Mich.) was induced by intraperitoneal injection with 100 LD_{50} (a 100-fold median lethal challenge corresponding to approximately 10^6 to 10^7 CFU) in 20% hog gastric mucin (Pfaltz and Bauer, Waterbury, Conn.) by using a 6-h *E. faecalis* culture grown in Trypticase soy broth (Difco Laboratories) at 37°C and resulted in 100% lethality in untreated mice by 24 h. Treatment with 0.5-ml drug volumes (10 animals per dose group) was by single subcutaneous (s.c.) abdominal injection at challenge or by oral (p.o.) gavage in 5% aqueous gum acacia (Mallinckrodt Chemical Company, Paris, Ken.) at challenge and 5 h later. The drug dose protecting 50% of the mice from lethal infection (PD_{50} [in milligrams per kilogram of body weight]) was calculated by probit analysis (11) and was expressed on a per drug dose basis. PD_{50}s were determined from duplicate tests with at least two common dose levels.

In studies characterizing the infection model, mice were sacrificed at 5 h postchallenge and heart blood and intraperitoneal fluid were collected; livers and kidneys were harvested, rinsed with saline, weighed, and pulverized (Lab Blender model 80 stomacher; Tekmar Company, Cinncinati, Ohio). Diluted specimens were plated on Trypticase soy agar with 5% sheep blood for CFU determinations after 24 to 48 h of incubation. Also, mice were necropsied 5 to 6 and 24 h postbacterial challenge. Following gross examination, liver, lung, kidney, heart, spleen, thymus, and sternal lymph node samples were collected, fixed in 10% formalin, and processed for light microscopy. Histologic sections were stained with hematoxylin and eosin, Brown-Brenn and MacCallum-Goodpasture tissue Gram stains, and Mallory's phosphotungstic acid hematoxylin stain for fibrin (10).

In vitro susceptibilities of *E. faecalis* ($n = 17$) were generally uniform for the new quinolones (Table 1), with MICs ranging from 0.06 to 0.125 μg/ml for clinafloxacin, 0.125 to 0.5 μg/ml for CI-990, and 0.06 to 0.25 μg/ml for PD 138312; values were higher for ciprofloxacin (the MIC at which 90% of the isolates

TABLE 2. Efficacy of clinafloxacin, CI-990, PD 138312 and comparative drugs in treatment of acute *E. faecalis* sepsis in mice[a]

E. faecalis strain	Drug	MIC (μg/ml)	PD_{50} (mg/kg) ± 95% confidence limits	
			PO	SC
MGH-2	Clinafloxacin	0.06	6.8 ± 3.0	2.1 ± 0.5
	CI-990[b]	0.125	18.5 ± 9.1	8.2 ± 2.2
	PD 138312	0.125	22.5 ± 10	1.6 ± 0.5
	Ciprofloxacin	0.5	41.0 ± 14.5	3.3 ± 1.2
	Vancomycin	2	NA[c]	10.0 ± 4.9
	Teicoplanin	0.5	NA	2.9 ± 0.6
	Ampicillin	1	13.3 ± 6.2	6.8 ± 3.7
	Gentamicin	16	NA	48.0 ± 23.4
	Ampicillin/gentamicin (10:1)[d]		NA	2.1 ± 0.75
WH-245 (β-lactamase producing)	Clinafloxacin	0.06	24.0 ± 8.1	2.3 ± 0.8
	CI-990	0.125	39.0 ± 21.0	7.1 ± 2.6
	PD 138312	0.125	76.0 ± 19.8	12.5 ± 5.9
	Ciprofloxacin	0.25	>100	9.4 ± 2.9
	Vancomycin	1	NA	6.7 ± 2.5
	Teicoplanin	0.25	NA	6.7 ± 2.4
	Ampicillin	2	>100	>100
	Gentamicin	32	NA	56.0 ± 23
	Ampicillin/gentamicin (10:1)[d]		NA	32.0 ±15.2
AIB-218 (vancomycin resistant)	Clinafloxacin	0.06	4.3 ± 1.3	1.1 ± 0.4
	CI-990	0.25	7.2 ± 2.3	2.1 ± 0.75
	PD 138312	0.125	7.2 ± 2.0	2.3 ± 0.8
	Ciprofloxacin	0.5	47.0 ± 16.4	4.3 ± 1.8
	Vancomycin	512	NA	>100
	Teicoplanin	0.5	NA	6.0 ± 1.1
	Ampicillin	2	33.0 ± 6.0	4.8 ± 1.0
	Gentamicin	16	NA	18.5 ± 2.6
	Ampicllin/gentamicin (10:1)[d]		NA	4.8 ± 1.5
WD-1592 (high-level gentamicin resistant)	Clinfloxacin	0.125	8.3 ± 1.8	1.5 ± 0.3
	CI-990	0.25	17.5 ± 5.3	1.9 ± 0.9
	PD 138312	0.125	10.5 ± 3.7	1.25 ± 0.75
	Ciprofloxacin	1	57.0 ± 32.9	3.1 ± 1.0
	Vancomycin	1	NA	5.2 ± 2.1
	Teicoplanin	0.5	NA	6.9 ± 3.1
	Ampicillin	2	>100	14.8 ± 6.2
	Gentamicin	>2,000	NA	>100
	Ampicillin/gentamicin (10:1)[d]		NA	17.5 ± 5.6
9J-2-U3 (ciprofloxacin resistant)	Clinafloxacin	2	>200	49.0 ± 24.5
	CI-990	8	>200	>200
	PD 138312	2	>200	39.5 ± 21.5
	Ciprofloxacin	32	>200	>200

[a] Infections were lethal in all untreated mice. Treatment was s.c. at the time of intraperitoneal challenge and p.o. at the time of challenge and 5 h later.
[b] PD 131628 parent used for MIC testing.
[c] NA, not applicable.
[d] PD_{50} values for ampicillin-gentamicin represent ampicillin doses.

were inhibited [MIC_{90}] = 1 μg/ml) and ofloxacin (MIC_{90} = 2 μg/ml). The activities of these quinolones were generally unchanged against one β-lactamase-producing, three high-level-gentamicin-resistant, and four vancomycin-resistant *E. faecalis* strains. Quinolone susceptibilities were substantially lower for 11 ciprofloxacin-resistant strains (the MIC_{90}s for clinafloxacin, CI-990, PD 138312, and ciprofloxacin were 8, 16, 32, and 64 μg/ml, respectively).

Against *Enterococcus faecium* (n = 10), quinolone activities that were four- to eightfold lower than those for the 17 *E. faecalis* strains described above were generally obtained and were unchanged against 12 vancomycin-resistant strains. Of these, one culture generated MICs of ciprofloxacin and ofloxacin of >128 μg/ml (the next resistant culture generated a MIC of ciprofloxacin of 4 μg/ml) compared with MICs of clinafloxacin, PD 138312, and CI-990 of 8, 16, and 32 μg/ml, respectively; these results corroborate an earlier report (2).

Clinafloxacin, CI-990, PD 138312, and ciprofloxacin were largely bactericidal (MBC-to-MIC ratios were generally ≤4) against four mouse-virulent *E. faecalis* cultures which consisted of typically susceptible (strain MGH-2), β-lactamase-producing (WH-245), vancomycin-resistant (AIB-218), and high-level gentamicin-resistant (WD-1592) isolates. The one exception was CI-990 versus WH-245 (MIC = 0.125 μg/ml; MBC = 8 μg/ml); CI-990 was bactericidal against seven additional β-lactamase-producing and five non-β-lactamase-producing *E. faecalis* cultures.

The presence of 50% heat-inactivated pooled human serum

had no influence on the inhibitory or bactericidal activities of the new fluoroquinolones against *E. faecalis* MGH-2 and ATCC 29212, while cefazolin, with a high level of serum protein-binding activity (9), displayed up to an eightfold loss of potency.

In single-step resistance studies, the new fluoroquinolones were comparable to ciprofloxacin; their frequencies of spontaneously resistant mutants were below the limits of detection (range, $<0.59 \times 10^{-11}$ to $<6.7 \times 10^{-11}$) for *E. faecalis* MGH-2 at four times the MIC. Multistep resistance rose in stepwise progression over 14 transfers for clinafloxacin (MICs increased from 0.06 to 32 μg/ml), CI-990 (0.125 to 32 μg/ml), PD 138312 (0.03 to 8 μg/ml), and ciprofloxacin (1 to 256 μg/ml) and increased at similar rates.

At 5 h postchallenge with approximately 2.5×10^6 *E. faecalis* MGH-2 CFU per mouse, viable counts were 1.0×10^{10} CFU per ml of intraperitoneal fluid (site of challenge), 1.0×10^6 CFU per ml of heart blood, 3.0×10^7 CFU per g of liver, and 2.6×10^8 CFU per g of kidney. Inoculation of mice with autoclaved or filtered supernatant from the bacterial suspension did not result in any deaths ($n = 10$). Upon histologic examination, acute lymphocytic necrosis and minimal margination of leukocytes within pulmonary or hepatic central veins were seen. Bacteria within macrophages were present within sternal lymph nodes. No nidus of infection or inflammation was evident.

The acute lethality of this *E. faecalis* infection model appears to be related to septicemic factors and not to parenchymal infection on account of seeding out of bacteria.

The efficacies of drugs protecting mice from induced lethal infections against five mouse-virulent *E. faecalis* strains were measured (Table 2).

Upon p.o. administration, the new fluoroquinolones were consistently more active than ciprofloxacin; specifically, PD_{50}s compared with those for ciprofloxacin, respectively, were 6.8 to 22 and 41 mg/kg against strain MGH-2, 24 to 76 and >100 mg/kg against WH-245, 4.3 to 7.2 and 47 mg/kg against AIB-218, and 8.3 to 17.5 and 57 mg/kg against WD-1592. In every case, clinafloxacin was somewhat more potent than CI-990 and PD 138312.

With s.c. administration, these four quinolones displayed comparable therapeutic activities: PD_{50}s ranged from 1.6 to 8.2 mg/kg against strain MGH-2, 2.3 to 12.5 mg/kg against WH-245, 1.1 to 4.3 mg/kg against AIB-218, and 1.25 to 3.1 mg/kg against WD-1592. Overall, clinafloxacin was more potent than the other quinolones against all enterococcal strains tested. Treatment of infection induced by the ciprofloxacin-resistant strain 9J-2-U3 (MIC, = 32 μg/ml) required PD_{50}s of 49 and 39 mg/kg for clinafloxacin and PD 138312, respectively, compared with values of >200 mg/kg for CI-990 and ciprofloxacin.

Average p.o./s.c. administration ratios obtained from these therapy tests (against ciprofloxacin-susceptible strains) were 5.7 for clinafloxacin, 5.1 for CI-990, 7.9 for PD 138312, and 13 for ciprofloxacin.

Contemporary concern over the emergence of drug-resistant enterococcal pathogens has prompted a search for alternative antimicrobial agents. A number of broad-spectrum quinolones possess activity against gram-positive bacterial species and display pharmacokinetic parameters indicating potential utility for therapy of systemic infections. The data presented in this report reveal high levels of in vitro activities (MIC_{90}s, ≤0.5 μg/ml) against *E. faecalis* for the new fluoroquinolones clinafloxacin, CI-990, and PD 138312, and our values are consistent with those reported earlier (1, 7, 12). In vitro clinafloxacin, CI-990, and PD 138312 activities were consistently severalfold higher than those of ciprofloxacin and ofloxacin.

The efficacies reported here indicate that the activities of clinafloxacin, CI-990, and PD 138312 after p.o. dosing were higher than those of ciprofloxacin against *E. faecalis* tester strains. The order of in vivo activity (clinafloxacin > CI-990 ~ PD 138312 > ciprofloxacin) followed the order of in vitro potencies. Clinafloxacin was also the most active drug by s.c. dosing, although all four fluoroquinolones were generally comparable in performance by this route of administration. The relatively low p.o./s.c. administration mean ratios of the newer fluoroquinolones (5.1 to 7.9 compared with 13 for ciprofloxacin) are in accord with the pharmacokinetic parameters reported in part elsewhere (3, 19) for mice who received a single dose of 50 mg/kg. The mean peak concentrations of drug in blood (C_{max}) obtained p.o. and s.c. (and bioavailability) were, respectively, 6.1 and 8.1 μg/ml (60%) for clinafloxacin, 7.0 and 12.3 μg/ml (54%) for CI-990, 2.2 and 8.6 μg/ml (20%) for PD 138312, and 2.3 and 8.4 μg/ml (11%) for ciprofloxacin. These animal study results provide support for the possibility that preliminary C_{max} values from single-dose p.o. and intravenous phase 1 clinical trials, which were 2.4 and 3.5 μg/ml for clinafloxacin and 1.7 and 3.4 μg/ml for CI-990 (17), respectively, may indicate clinical utility against enterococci for these new quinolones.

In summary, there may be no therapeutic options for patients infected with multiply resistant enterococci. The MICs of the new fluoroquinolones against enterococci were lower and the bioavailability values were higher than those of ciprofloxacin. Overall, the efficacy of quinolones in this sepsis model, in decreasing order, was as follows: clinafloxacin, CI-990, PD 138312, and ciprofloxacin. Although clinical confirmation is needed, clinafloxacin, CI-990, and PD 138312 may have therapeutic potential in systemic enterococcal infections in humans.

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