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Comparative In Vitro Activity of PD 127,391, a New Fluorinated 4-Quinolone Derivative

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PD 127,391, a newly developed 4-quinolone chemically similar to ciprofloxacin, was studied in vitro by using agar and broth dilution and two inoculum sizes. PD 127,391 was found to be highly active against gram-negative aerobes, including *Pseudomonas aeruginosa* and other *Pseudomonas* spp. Its activity against gram-positive aerobes was better than that of ciprofloxacin.

PD 127,391 (7-[3-amino-1-pyrrolidinyl]-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinololinecarboxylic acid) is a recently developed, 8-substituted fluorinated 4-quinolone (4). Its chemical structure is similar to that of ciprofloxacin (Fig. 1).

In this study, the in vitro activities of PD 127,391 against clinical isolates of aerobic and microaerophilic bacterial strains were compared with those of ciprofloxacin, ceftazidime, gentamicin, and imipenem by using agar and broth dilution. Also evaluated were the effects of varying the bacterial inoculum sizes used.

(This study was presented at the 6th Mediterranean Congress of Chemotherapy Taormina, Italy, 22 to 27 May 1988.)

All bacterial strains tested were clinical isolates collected from hospitalized patients or out-patients. No patient provided more than one strain, and caution was taken to avoid collection of more than one strain of any species from the same hospital ward.

PD 127,391 was obtained from Warner-Lambert Co., Ann Arbor, Mich.; ciprofloxacin was kindly supplied by Bayer AG, Leverkusen, Federal Republic of Germany; ceftazidime was provided by Glaxo Group Research Ltd., Greenford, Middlesex, England; gentamicin was provided by Schering Corp., Kenilworth, N.J.; and imipenem was provided by Merck Sharp & Dohme, Rahway, N.J. All antibiotics were provided with known potencies.

The medium used was Mueller-Hinton agar or broth (E. Merck AG, Darmstadt, Federal Republic of Germany). When gram-positive bacteria were tested, 5% lysed citrated horse blood was added. For *Haemophilus influenzae*, McLeod GC agar base (36 g/1,000 ml; Difco Laboratories, Detroit, Mich.) and Bacto-Agar (1 g/1,000 ml; Difco), supplemented with 1% hemoglobin powder (Oxoid Ltd., London, England) and 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.), were used. A stock solution of PD 127,391 (10 mg/ml) was prepared by dissolving it in 0.5 ml of dimethylacetamide and diluting it in sterile water.

Agar dilution MICs were determined by incorporating the antibiotics into the medium in twofold dilutions ranging from 0.03125 to 64 μg/ml. Overnight cultures were inoculated onto agar plates with a diameter of 8.5 cm by using a modified Steer replicator (Denley Instruments, Sussex, England). Each strain was tested at two inoculum sizes, 10^4 and 10^6 CFU per application. The agar plates were incubated overnight at 37°C, and MICs, the lowest antibiotic concentrations that completely inhibited visible growth, were determined.

Five to ten strains of gram-negative species were selected for the testing of broth dilution MICs by using 1 ml of broth for each test. Antibiotics were added to give final concentrations ranging from 0.03125 to 64 μg/ml. The inoculum used was 10^6 CFU/ml. MICs, the lowest antibiotic concentrations completely inhibiting visible growth, were determined after overnight incubation at 37°C. MBCs were assayed by transferring 0.1 ml of broth from tubes without visible growth to agar plates, by incubating at 37°C overnight, and by determining the lowest antibiotic concentration killing 99.9% of the organisms.

When the agar dilution technique was used for MIC determinations, PD 127,391 was highly active, with minimum inoculum dependence, against all strains of gram-negative aerobic and microaerophilic species tested. The MICs for 90% of the strains tested (MIC_{90}s) were below 0.125 μg/ml for most organisms (Table 1). Notably, all strains of *Pseudomonas aeruginosa* and *Pseudomonas* spp. were inhibited by 0.5 μg/ml or less of PD 127,391 at both the low and high inocula. In comparison with ciprofloxacin, there were no major differences in activities against these species. At the high inoculum, four strains of *Shigella* spp. were inhibited at concentrations ranging from 0.03 to 0.5 μg/ml and six strains of *Providencia* spp. were inhibited at concentrations between 0.03 and 0.25 μg/ml. Against gram-positive aerobes, PD 127,391 was considerably more active than ciprofloxacin and inhibited all strains of staphylococci and streptococci other than *Streptococcus faecalis* at concentrations of 0.13 μg/ml or less, while up to 4 μg of ciprofloxacin per ml was required to inhibit these strains. When the high inoculum was used against *S. faecalis*, the MIC_{90} of PD 127,391 was 0.25 μg/ml and the MIC_{90} of ciprofloxacin was 0.5 μg/ml. Both antibiotics inhibited all strains at 1 μg/ml. In comparison with the other antibiotics

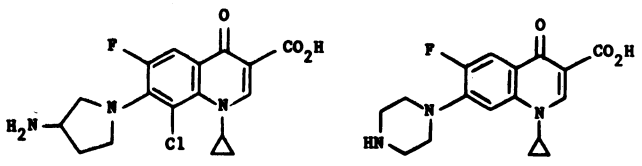

FIG. 1. Chemical structures of PD 127,391 (left) and ciprofloxacin (right).

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TABLE 1. MICs of PD 127,391, ciprofloxacin, ceftazidime, gentamicin, and imipenem when tested in agar dilution

Bacterial species (no. of strains)	Antibiotic	MIC (μg/ml) at:					
		10^4 CFU/application			10^6 CFU/application		
		Range	50%[a]	90%	Range	50%	90%
Escherichia coli (40)	PD 127,391	≤0.03–0.06	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ciprofloxacin	≤0.03–0.06	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ceftazidime	≤0.03–0.13	0.06	0.06	≤0.03–0.25	0.13	0.13
	Gentamicin	0.13–2	0.25	0.5	0.25–4	0.5	0.5
	Imipenem	0.06–1	0.13	0.25	0.25–8	0.5	0.5
Klebsiella pneumoniae (19)	PD 127,391	≤0.03–0.13	≤0.03	0.13	≤0.03–0.25	≤0.03	0.25
	Ciprofloxacin	≤0.03–0.5	≤0.03	0.5	≤0.03–1	0.06	1
	Ceftazidime	≤0.03–32	0.13	0.5	0.13–>64	0.25	0.5
	Gentamicin	0.06–0.5	0.25	0.5	0.13–0.5	0.5	0.5
	Imipenem	0.25–1	0.25	0.5	0.5–8	1	2
Klebsiella spp. (19)	PD 127,391	≤0.03–0.25	≤0.03	≤0.03	≤0.03–0.5	≤0.03	0.13
	Ciprofloxacin	≤0.03–0.25	≤0.03	≤0.03	≤0.03–1	≤0.03	≤0.03
	Ceftazidime	≤0.03–0.25	0.06	0.06	0.06–0.5	0.13	0.25
	Gentamicin	0.13–0.25	0.25	0.25	0.25–0.5	0.5	0.5
	Imipenem	0.13–0.25	0.25	0.25	0.5–2	1	1
Enterobacter spp. (20)	PD 127,391	≤0.03–0.25	≤0.03	0.13	≤0.03–0.25	≤0.03	≤0.03
	Ciprofloxacin	≤0.03–1	≤0.03	0.25	≤0.03–0.5	≤0.03	0.06
	Ceftazidime	≤0.03–32	0.13	0.25	0.06–64	0.13	0.25
	Gentamicin	0.25–1	0.25	0.5	0.25–0.5	0.5	0.5
	Imipenem	0.13–4	0.25	1	0.5–8	1	8
Salmonella spp. (20)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	≤0.03–0.06	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ceftazidime	0.13–0.5	0.13	0.25	0.13–0.5	0.13	0.5
	Gentamicin	0.13–8	0.25	0.25	0.25–16	0.25	0.5
	Imipenem	0.13–0.5	0.25	0.5	0.5–1	0.5	1
Proteus mirabilis (19)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ciprofloxacin	≤0.03–0.06	≤0.03	≤0.03	≤0.03–0.13	≤0.03	0.06
	Ceftazidime	≤0.03–0.06	≤0.03	≤0.03	≤0.03–4	0.13	4
	Gentamicin	0.13–0.5	0.25	0.5	0.25–1	0.5	1
	Imipenem	0.25–2	0.25	0.5	1–8	4	8
Proteus spp. (8)	PD 127,391	≤0.03–0.13	≤0.03		≤0.03–0.13	≤0.03	
	Ciprofloxacin	≤0.03–0.06	≤0.03		≤0.03–0.13	≤0.03	
	Ceftazidime	≤0.03–0.06	≤0.03		≤0.03–2	1	
	Gentamicin	0.13–2	0.25		0.5–8	1	
	Imipenem	0.25–2	0.5		4–64	8	
Morganella morganii (10)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	≤0.03	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ceftazidime	≤0.03–4	0.06	0.5	≤0.03–8	0.13	0.5
	Gentamicin	0.13–2	0.25	0.5	0.5–2	0.5	1
	Imipenem	0.5–2	1	2	2–16	8	8
Pseudomonas aeruginosa (20)	PD 127,391	≤0.03–0.5	0.13	0.25	0.06–0.5	0.13	0.5
	Ciprofloxacin	≤0.03–1	0.13	1	0.06–1	0.13	1
	Ceftazidime	0.5–2	1	2	0.5–8	2	2
	Gentamicin	0.5–4	1	4	1–8	2	4
	Imipenem	0.5–4	2	4	0.5–8	2	8
Pseudomonas spp. (11)	PD 127,391	≤0.03–0.25	0.13	0.25	≤0.03–0.25	0.13	0.25
	Ciprofloxacin	≤0.03–0.25	0.13	0.25	≤0.03–1	0.13	0.5
	Ceftazidime	0.5–2	1	2	1–4	1	2
	Gentamicin	0.5–4	2	4	1–4	2	4
	Imipenem	0.13–32	1	32	0.25–32	1	32
Yersinia spp. (10)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ceftazidime	≤0.03–0.25	≤0.03	0.06	≤0.03–1	0.06	0.13
	Gentamicin	≤0.03–0.25	0.06	0.25	0.13–0.5	0.5	0.5
	Imipenem	≤0.03–0.5	0.25	0.5	0.25–4	0.25	2

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TABLE 1—*Continued*

Bacterial species (no. of strains)	Antibiotic	MIC (μg/ml) at:					
		10^4 CFU/application			10^6 CFU/application		
		Range	50%[a]	90%	Range	50%	90%
Haemophilus influenzae (12)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	≤0.03	≤0.03	≤0.03	≤0.03–0.06	≤0.03	≤0.03
	Ceftazidime	≤0.03–0.06	0.06	0.06	0.13	0.13	0.13
	Gentamicin	0.25–1	0.5	1	1–2	1	1
	Imipenem	0.06–1	1	1	8–32	8	16
Branhamella catarrhalis (9)	PD 127,391	≤0.03	≤0.03		≤0.03	≤0.03	
	Ciprofloxacin	≤0.03	≤0.03		≤0.03–0.13	0.06	
	Ceftazidime	≤0.03	≤0.03		≤0.03–0.13	≤0.03	
	Gentamicin	0.13–0.5	0.25		0.25–0.5	0.5	
	Imipenem	≤0.03–0.06	≤0.03		≤0.03–0.13	0.06	
Staphylococcus aureus, penicillin susceptible (8)	PD 127,391	≤0.03	≤0.03		≤0.03	≤0.03	
	Ciprofloxacin	0.13–0.25	0.25		0.25	0.25	
	Ceftazidime	4–8	4		8–16	8	
	Gentamicin	0.25–1	0.5		0.5–1	0.5	
	Imipenem	≤0.03	≤0.03		≤0.03–0.06	≤0.03	
Staphylococcus aureus, penicillinase producing (20)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	0.13–0.25	0.25	0.25	0.13–0.25	0.25	0.25
	Ceftazidime	4–8	8	8	8	8	8
	Gentamicin	0.25–1	0.25	0.5	0.5–1	0.5	1
	Imipenem	≤0.03–0.06	≤0.03	0.06	≤0.03–0.06	0.06	0.06
Staphylococcus epidermidis, penicillinase producing (10)	PD 127,391	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
	Ciprofloxacin	0.13–0.25	0.25	0.25	0.25	0.25	0.25
	Ceftazidime	4–64	13	32	4–>64	16	>64
	Gentamicin	0.06–>64	0.5	>64	0.13–>64	1	>64
	Imipenem	≤0.03–>64	1	4	≤0.03–>64	16	>64
Staphylococcus epidermidis, methicillin resistant (9)	PD 127,391	≤0.03	≤0.03		≤0.03	≤0.03	
	Ciprofloxacin	0.13–0.25	0.25		0.13–0.25	0.25	
	Ceftazidime	8–>64	32		32–>64	64	
	Gentamicin	0.06–>64	>64		0.13–>64	>64	
	Imipenem	0.5–>64	2		8–>64	>64	
Streptococcus faecalis (15)	PD 127,391	0.06–0.13	0.13	0.13	0.06–1	0.25	0.25
	Ciprofloxacin	0.25–0.5	0.25	0.5	0.25–1	0.5	1
	Ceftazidime	16–>64	32	>64	>64	>64	>64
	Gentamicin	1–32	4	4	4–16	8	16
	Imipenem	1–2	2	2	2–4	2	4
Streptococcus pyogenes (9)	PD 127,391	≤0.03–0.06	≤0.03		0.06	0.06	
	Ciprofloxacin	0.25–0.5	0.25		0.25–1	0.5	
	Ceftazidime	≤0.03	≤0.03		≤0.03	≤0.03	
	Gentamicin	2–4	4		4–8	8	
	Imipenem	≤0.03	≤0.03		≤0.03	≤0.03	
Streptococcus agalactiae (7)	PD 127,391	0.06–0.13	0.06		0.06–0.13	0.13	
	Ciprofloxacin	0.5–2	0.5		0.5–4	1	
	Ceftazidime	0.25–1	0.25		0.25–2	0.5	
	Gentamicin	1–16	16		16–32	32	
	Imipenem	≤0.03	≤0.03		≤0.03–0.06	0.06	
Viridans group streptococci (8)	PD 127,391	0.06–0.13	0.06		0.06–0.13	0.13	
	Ciprofloxacin	1–4	2		1–4	2	
	Ceftazidime	0.06–>64	0.5		0.25–>64	>64	
	Gentamicin	0.25–16	2		1–16	8	
	Imipenem	≤0.03–4	≤0.03		≤0.03–4	0.06	

[a] 50%, MIC for 50% of the strains tested.

tested, PD 127,391 was active against ceftazidime-resistant strains of viridans group streptococci and staphylococci, as well as against imipenem-resistant staphylococcal strains and gentamicin-resistant streptococci. In addition, for four strains of *Listeria monocytogenes* PD 127,391 MICs were 0.13 μg/ml at the low inoculum and 0.25 μg/ml at the high inoculum. Corresponding values for ciprofloxacin were 2 μg/ml at both inocula. At the high inoculum, six strains of

Staphylococcus saprophyticus were all inhibited by 0.13 μg of PD 127,391 per ml and 1 μg of ciprofloxacin per ml.

The in vitro activity of PD 127,391 was not affected by the technique used for MIC determinations, and MBCs were similar to MICs at both the low and high inocula. In general, higher MBC/MIC ratios were found for the comparative drugs, including ciprofloxacin, than for PD 127,391. Thus, for six strains of *Pseudomonas* spp., the MBC/MIC ratios ranged between 1 and 2 for PD 127,391 and between 2 and 64 for ciprofloxacin (median values, 1 and 9, respectively).

This study demonstrated an improved antibacterial activity of PD 127,391, in comparison with ciprofloxacin, against gram-positive bacterial pathogens, while the two quinolones were comparable in their activities against the gram-negative strains tested. Both PD 127,391 and ciprofloxacin were highly active against several gram-positive strains resistant to ceftazidime, gentamicin, or imipenem. The results obtained with ciprofloxacin, ceftazidime, gentamicin, and imipenem were similar to those previously reported (1–3, 5).

Before any conclusions can be drawn as to the clinical usefulness of PD 127,391, data must be gathered on its animal toxicology and its disposition and safety in humans. However, from its in vitro antibacterial activity, further studies of this new fluorinated quinolone are worthwhile.

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