ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1994, p. 611–615
0066-4804/94/$04.00+0

Vol. 38, No. 3

Comparative In Vitro Activity of DU-6859a, a New Fluoroquinolone Agent, against Gram-Positive Cocci

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Received 27 September 1993/Returned for modification 23 November 1993/Accepted 4 January 1994

The in vitro activity of DU-6859a (DU), a new fluoroquinolone agent, was evaluated against 233 gram-positive cocci and was compared with those of ciprofloxacin, vancomycin, nafcillin, and ampicillin. The MICs of DU for 90% of the staphylococci tested were ≤0.06 μg/ml. All of the groups A and B and viridans group streptococci were inhibited by ≤0.125 μg of DU per ml, which was 32-fold more active than ciprofloxacin. On the basis of MICs for 90% of the strains tested, DU was 32- and 16-fold more active than ciprofloxacin against *Enterococcus faecalis* and *Enterococcus faecium*, respectively. The bactericidal activity of DU was demonstrated by time-kill techniques against all ciprofloxacin-susceptible enterococci. DU shows promise for the treatment of infections with gram-positive cocci and warrants further evaluation by in vitro and in vivo studies.

Many fluoroquinolone agents have excellent in vitro activities against members of the family *Enterobacteriaceae* and against *Pseudomonas aeruginosa* (29). DU-6859a (DU) is a new fluoroquinolone antimicrobial agent with the chemical structure 7-[(7*S*)-7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fluoro-1-[(1*R*,2*S*)-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid sesquihydrate (25). Since the presently available fluoroquinolone agents possess only moderate activities against many gram-positive bacteria, recent efforts have been directed toward the synthesis of compounds which have greater activities against these organisms, such as tosufloxacin (1), sparfloxacin (1, 3, 9), CI-934 (4), WIN 57273 (7, 15, 17), PD 117596 (5), PD 127391 (CI-960) (5, 9, 20), PD 131628 (9), T-3761 (10), OPC-17116 (14), AM-1155 (13), E-4497 (11), CP-74667 (16), and CP-99219 (6). DU appears to be one of the most active of these agents (25). In the present study, the antibacterial activity of DU was investigated and compared with the activities of ciprofloxacin, vancomycin, nafcillin, and ampicillin against gram-positive cocci representing a broad range of antimicrobial resistance patterns.

DU in powder form was provided by Daiichi Pharmaceutical Co., Tokyo, Japan; ciprofloxacin was provided by Miles Pharmaceuticals, West Haven, Conn.; and vancomycin, nafcillin, and ampicillin were purchased from Sigma Chemical Co., St. Louis, Mo. All staphylococci and streptococci were collected from hospitals in Houston, Tex., between 1989 and 1992. Some of the enterococci used for this study were part of a stock collection and were originally isolated in Thailand and Chile in the early 1980s (21). Some of the high-level ampicillin-resistant *Enterococcus faecium* isolates and β-lactamase-producing and/or high-level gentamicin-resistant *Enterococcus faecalis* isolates were recovered in the last 7 years and were provided to us by other sources from Connecticut, California, Florida, Delaware, Massachusetts, Wisconsin, Virginia, the Centers for Disease Control, and Argentina (19, 22). Vancomycin-resistant *E. faecium* isolates were kindly provided by S. Handwerger, New York (12), and P. van der Auwera, Brussels, Belgium; others were isolated in Houston, Tex.

The MICs for a total of 233 clinical bacterial isolates were determined with DU, ciprofloxacin, and one or more of vancomycin, ampicillin, and nafcillin. The MIC was defined as the lowest concentration of antibiotic which inhibited growth on Mueller-Hinton agar after 24 h of incubation at 37°C. MICs were determined by a standard twofold dilution technique in Mueller-Hinton agar, which was supplemented with 5% defibrinated sheep blood when streptococci were tested according to the guidelines of the National Committee for Clinical Laboratory Standards (23). For inoculum preparation, Mueller-Hinton broth was used for all isolates, except that it was adjusted to contain Ca (50 mg/liter) and Mg (25 mg/liter) for streptococci. The final inoculum was approximately 10^4 CFU per spot. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, and *E. faecalis* ATCC 29212 were used as control strains.

The bactericidal activity of DU against 7 *E. faecalis* and 3 *E. faecium* isolates was determined. Overnight cultures were diluted to yield a final inoculum of ~10^7 CFU/ml in flasks containing brain heart infusion broth. The concentration of DU (2 μg/ml) used in the time-kill assays was recommended by the manufacturer to represent levels achievable in human serum. Samples (100 μl each) were withdrawn from flasks following 0, 4, and 24 h of incubation at 37°C with agitation. Undiluted and serially diluted samples were plated onto brain heart infusion agar plates. The lowest detectable number of organisms was 10 CFU/ml. The agar plates were incubated at 37°C for 24 h before CFU were counted. Bactericidal activity was defined as a reduction in CFU of >3 $\log_{10}$. A drug carryover effect was excluded by showing that there was less than 5% difference in colony counts when 100 μl of 10^3 to 10^4 CFU/ml was plated onto antibiotic-free plates in the absence or presence of DU (2 μg/ml).

The results of susceptibility testing with DU and a comparison of these results with the results of testing with other antibiotics are shown in Table 1. Fifty percent of the staphylococcal isolates tested were inhibited by ≤0.03 μg of DU per ml, and 90% were inhibited by ≤0.06 μg/ml (Table 1). The MICs for 90% of strains tested (MIC_{90}s) were higher for the methicillin-resistant subgroups of *S. aureus* and coagulase-negative staphylococci than for the methicillin-susceptible sub-

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TABLE 1. Comparative in vitro activity of DU-6859a against staphylococci, enterococci, and streptococci

Species or type of organism (no. of isolates)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
S. aureus (53)	DU	0.007–2	0.03	0.06
	Ciprofloxacin	0.06–128	0.25	0.5
	Vancomycin	0.5–2	1	1
	Nafcillin	0.25–>64	0.5	>64
Methicillin resistant (24)	DU	0.007–2	0.03	1
	Ciprofloxacin	0.125–128	0.25	128
	Vancomycin	0.5–2	1	1
	Nafcillin	32–>64	64	>64
Methicillin susceptible (29)	DU	0.007–0.06	0.015	0.03
	Ciprofloxacin	0.06–0.5	0.25	0.5
	Vancomycin	1–2	1	1
	Nafcillin	0.25–1	0.25	0.5
Coagulase-negative staphylococci (52)	DU	0.007–0.5	0.015	0.03
	Ciprofloxacin	0.06–64	0.125	1
	Vancomycin	0.25–2	1	2
	Nafcillin	0.25–>64	1	>64
Methicillin resistant (23)	DU	0.007–0.5	0.015	0.125
	Ciprofloxacin	0.06–64	0.25	8
	Vancomycin	1–2	2	2
	Nafcillin	1–>64	32	>64
Methicillin susceptible (29)	DU	0.007–0.03	0.015	0.015
	Ciprofloxacin	0.06–2	0.125	0.25
	Vancomycin	0.25–2	1	2
	Nafcillin	0.015–8	0.25	4
E. faecalis (38)	DU	0.06–4	0.125	1
	Ciprofloxacin	0.5–64	1	32
	Vancomycin	1–2	1	1
	Ampicillin	1–16	2	4
β-Lactamase producers[a] (12)	DU	0.06–4	0.06	1
	Ciprofloxacin	0.5–64	0.5	32
	Vancomycin	1–2	1	2
	Ampicillin	2–4	2	4
Highly gentamicin resistant (12)	DU	0.06–1	0.125	1
	Ciprofloxacin	0.5–64	1	32
	Vancomycin	1–2	1	1
	Ampicillin	1–8	2	2
Other (14)	DU	0.06–0.25	0.125	0.25
	Ciprofloxacin	0.5–4	1	2
	Vancomycin	1	1	1
	Ampicillin	1–16	1	16
E. faecium (33)	DU	0.03–4	0.25	0.5
	Ciprofloxacin	0.5–32	2	8
	Vancomycin	0.5–>512	4	>512
	Ampicillin	0.5–512	8	256
Vancomycin resistant[b] (16)	DU	0.03–4	0.25	2
	Ciprofloxacin	0.5–32	2	32
	Vancomycin	32–>512	512	>512
	Ampicillin	8–256	16	256
Other (17)	DU	0.03–0.25	0.25	0.5
	Ciprofloxacin	0.5–4	2	4
	Vancomycin	0.5–4	1	2
	Ampicillin	0.5–64	4	16

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TABLE 1—*Continued*

Species or type of organism (no. of isolates)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Enterococcus spp.[c] (14)	DU	0.015–0.25	0.125	0.25
	Ciprofloxacin	0.25–2	1	2
	Vancomycin	2–512	8	256
	Ampicillin	0.25–2	0.5	2
Beta-hemolytic streptococci				
Group A streptococci (11)	DU	0.015–0.03	0.015	0.03
	Ciprofloxacin	0.25–2	0.5	2
	Ampicillin	0.015–0.5	0.015	0.06
Group B streptococci (13)	DU	0.03–0.06	0.03	0.06
	Ciprofloxacin	0.5–1	1	1
	Ampicillin	0.06–0.125	0.125	0.125
Viridans group streptococci (19)	DU	0.015–0.125	0.06	0.125
	Ciprofloxacin	0.5–4	2	2
	Ampicillin	0.015–16	1	8

[a] A total of 11 of the 12 isolates were also highly resistant to gentamicin (>500 μg/ml).
[b] A total of 8 of the 16 isolates were also highly resistant to gentamicin (>500 μg/ml) and ampicillin (≥64 μg/ml).
[c] Six *Enterococcus gallinarum*, three *Enterococcus durans*, and five *Enterococcus casseliflavus* isolates.

groups, presumably because of the presence of more isolates resistant to ciprofloxacin in these subgroups and because isolates for which the MICs of ciprofloxacin are higher also show higher MICs of DU. Although ciprofloxacin-resistant (MIC, 8 to 128 μg/ml), methicillin-resistant *S. aureus* isolates required higher MICs of DU, they were still inhibited by ≤2 μg/ml. DU was eightfold more active than ciprofloxacin against *E. faecalis*, including β-lactamase producers and high-level gentamicin-resistant isolates with a MIC_{50} of 0.125 μg/ml (Table 1). Fifty percent of *E. faecium* isolates were inhibited by a slightly higher concentration of DU (0.25 μg/ml), whereas the MIC_{50} was 2 μg/ml for ciprofloxacin. DU inhibited 90% of group A and group B streptococci at ≤0.06 μg/ml, making it 32 times more active than ciprofloxacin and comparable to ampicillin in its activity (Table 1). The MICs for viridans group streptococci were higher than those for the group A and group B streptococci. Ninety percent of viridans group streptococci were inhibited by 0.125 μg of DU per ml; the MIC_{90} of DU was 16-fold less than the MIC_{90} of ciprofloxacin.

The bactericidal activity of DU was tested by time-kill assays against 10 enterococcal isolates, including some multiresistant *E. faecalis* and *E. faecium* isolates. The resistance phenotypes of those strains and the magnitude of killing by DU are listed in Table 2. DU was bactericidal (≥99.9% reduction in CFU/ml) at 24 h, except for the one *E. faecalis* isolate with high-level ciprofloxacin resistance. DU was not bactericidal against this *E. faecalis* isolate; however, the isolate showed a 2.8 $\log_{10}$ reduction in colony counts at 24 h at the concentration corresponding to 2× the MIC (Fig. 1A). Rapid killing (>3 $\log_{10}$ at 4 h) against five *E. faecalis* isolates which are more susceptible to DU (MIC, ≤0.06 μg/ml) was observed (Fig. 1B). Killing was not different with β-lactamase-producing and/or high-level gentamicin-resistant isolates. Three *E. faecium* isolates and one *E. faecalis* isolate showed slower kinetics of killing (<3 $\log_{10}$ at 4 h) (Fig. 1A). However, the degree of killing by DU was still high after 24 h of exposure (5.7 ± 0.7 $\log_{10}$), regardless of the kinetics of bacterial killing for the nine ciprofloxacin-susceptible isolates. In several studies, cipro-

TABLE 2. Resistance phenotypes of enterococcal isolates used in time-kill studies and killing of enterococci by DU-6859a

Strain	Resistance phenotype		MIC (μg/ml)				Initial inoculum ($\log_{10}$)	Reduction from baseline ($\log_{10}$)	
	Bla$^+$	HLGR	Van	Amp	DU-6859a	Cip		4 h	24 h
E. faecalis									
E 47	+	+	2	2	0.06	0.5	7.2	−4.6	−5.7
WH 257	+	+	1	2	0.03	0.5	7.2	−4.9	−4.9
Fla #2	+	+	1	4	1.0	32	7.0	−1.4	−2.8
HG 1113	−	−	1	2	0.06	0.5	7.8	−5.7	−≥6.8[b]
MCP 273	−	+	1	1	0.12	0.5	7.4	−2.8	−5.8
HG 1118	−	+	1	1	0.06	0.5	7.3	−5.6	−6.3
V 2-5	−	−	2	1	0.06	0.5	7.5	−5.5	−≥6.5[a]
E. faecium									
VR 3	−	+	512	256	0.25	2	7.1	−2.0	−5.1
VR 16	−	−	512	128	0.25	2	7.3	−1.9	−5.5
57	−	−	>512	8	0.06	0.5	6.8	−1.5	−5.1

[a] Abbreviations: Bla$^+$, β-lactamase producing; HLGR, high-level gentamicin resistant (MIC, ≥500 μg/ml); Van, vancomycin; Amp, ampicillin; Cip, ciprofloxacin.
[b] The lowest number of detectable CFU/ml was 10.

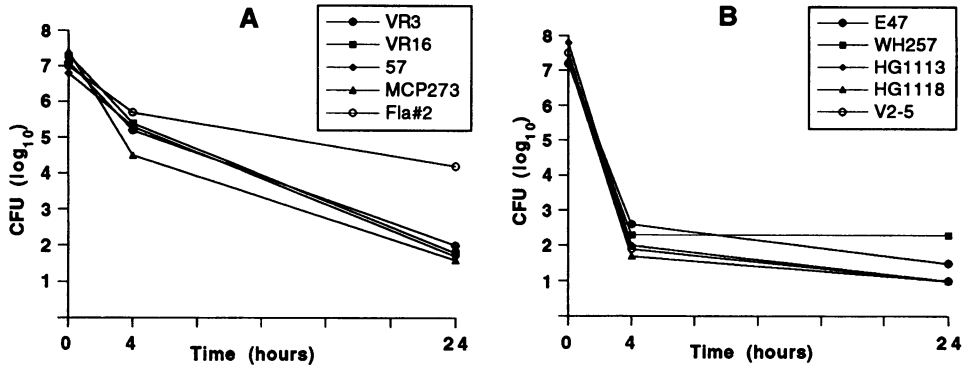

FIG. 1. Bactericidal activity of DU-6859a against enterococci. (A) Time-kill curves showing the in vitro activity of 2 μg of DU-6859a per ml against a ciprofloxacin-resistant *E. faecalis* isolate (Fla#2) and three *E. faecium* and one *E. faecalis* isolates which showed a lower rate of killing than those of the strains in panel B; (B) time-kill curves showing the in vitro activity of 2 μg of DU-6859a per ml against five *E. faecalis* isolates that were more rapidly killed by DU.

floxacin was not found to be bactericidal against enterococci at one to four times the MIC at 24 h (8, 27, 28). WIN 57273, a new investigational fluoroquinolone which has low MICs against gram-positive organisms, was also not bactericidal against staphylococci and *E. faecalis* (7). In another study, 2 μg of WIN 57273 per ml demonstrated bactericidal activity against five of the six enterococcal isolates at 24 h (17). Lewin et al. showed that the rates of killing by ciprofloxacin, ofloxacin, and DR-3355 against *E. faecalis* were lower than those against staphylococci or *Enterobacteriaceae* (18). Those agents were not bactericidal against either *E. faecalis* ATCC 19433 or a clinical isolate after 3 h of exposure; however, after 24 h of exposure, they were bactericidal, and the degree of killing was similar for enterococci and staphylococci (18). Similarly to our findings, Sahm and Koburov noted a ≥ 3 $\log_{10}$ reduction in CFU at 24 h for CI-934 and for ciprofloxacin against some enterococci but not for the two strains for which the MICs of ciprofloxacin and CI-934 were ≥ 4 μg/ml (24). Even when bactericidal activity was present at 24 h, there was usually <3 $\log_{10}$ killing at 4 h. Further studies are needed to clarify whether slow or rapid bactericidal activities of quinolones against enterococci are related to initial levels of susceptibility, to species and/or strain differences, or to the pharmacologic properties of different agents.

The results of this study demonstrated that DU inhibits gram-positive species at low concentrations (≤ 0.06 μg/ml for most staphylococci and ≤ 0.125 μg/ml for streptococci). This potency is greater than that of ciprofloxacin. Enterococci appear less susceptible than staphylococci and streptococci, although the MIC_{90}s were 8- to 32-fold less than those of ciprofloxacin. DU inhibited 90% of vancomycin-resistant *E. faecium* isolates, organisms for which the therapeutic options are extremely limited, at concentrations of ≤ 2 μg/ml. The resistance of *S. aureus* and enterococci to fluoroquinolones has increased remarkably in recent years (2, 26). Highly ciprofloxacin-resistant isolates of staphylococci and enterococci also required higher MICs of DU, although the values were ≤ 4 μg/ml. Although comparison of different studies using organisms from different sources has to be made cautiously, on the basis of published data showing the activities of other new fluoroquinolones, DU demonstrated activity equal to or higher than those of these agents against most gram-positive cocci (1, 3–7, 9–11, 13–17, 19). Our study suggests that DU may prove useful in infections caused by gram-positive cocci. Further studies of the pharmacokinetics, toxicologic evaluation, and clinical efficacy of this drug are warranted.

This work was supported by a grant from Daiichi Pharmaceutical Co., Tokyo, Japan.

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