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In Vitro and In Vivo Antibacterial Efficacies of CFC-222, a New Fluoroquinolone

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CFC-222 is a novel fluoroquinolone containing a C-7 bicyclic amine moiety with potent antibacterial activities against gram-positive, gram-negative, and anaerobic organisms. We compared the in vitro and in vivo activities of CFC-222 with those of ciprofloxacin, ofloxacin, and lomefloxacin. CFC-222 was more active than the other fluoroquinolones tested against gram-positive bacteria. CFC-222 was particularly active against *Streptococcus pneumoniae* (MIC at which 90% of isolates are inhibited [MIC_{90}], 0.2 μg/ml), *Staphylococcus aureus* (MIC_{90}, 0.2 μg/ml for ciprofloxacin-susceptible strains), and *Enterococcus faecalis* (MIC_{90}, 0.39 μg/ml). Against *Escherichia coli* and other members of the family *Enterobacteriaceae*, CFC-222 was slightly less active than ciprofloxacin (MIC_{90}s for *E. coli*, 0.1 and 0.025 μg/ml, respectively). The in vitro activity of CFC-222 was not influenced by inoculum size, medium composition, or the presence of horse serum. However, its activity was decreased significantly by a change in the pH of the medium from 7.0 to 6.0, as was the case for the other quinolones tested. The in vivo protective efficacy of CFC-222 by oral administration was greater than those of the other quinolones tested in a mouse model of intraperitoneally inoculated systemic infection caused by *S. aureus*. CFC-222 exhibited efficacy comparable to that of ciprofloxacin in the same model of infection caused by gram-negative organisms, such as *E. coli* and *Klebsiella pneumoniae*. In this infection model, CFC-222 was slightly less active than ciprofloxacin against *Pseudomonas aeruginosa*. These results suggest that CFC-222 may be a promising therapeutic agent in various bacterial infections.

Fluoroquinolone antibacterial agents have been characterized by potent and broad-spectrum antibacterial activities. A number of fluoroquinolone derivatives such as ciprofloxacin, ofloxacin, lomefloxacin, sparfloxacin, and tosufloxacin have been used for the treatment of various serious infectious diseases. However, these agents either exhibit restricted antibacterial activity against staphylococci and streptococci or have somewhat unfavorable pharmacokinetic characteristics, for example, relatively short half-lives in serum. Most of them show excellent oral bioavailability. Recent research related to the development of new fluoroquinolone animicrobial agents has been directed at expanding the antibacterial efficacy of ciprofloxacin toward gram-positive bacteria and anaerobic bacteria and improving its pharmacokinetic profile while retaining its excellent activity against gram-negative bacteria (1, 4, 12, 13, 15).

CFC-222, 7-([1α,5α,6β]-6-amino-1-methyl-3-azabicyclo[3.2.0]heptan-3-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid hydrochloride trihydrate (Fig. 1), is a novel fluoroquinolone antibacterial agent with a new bicyclic amine moiety at the 7 position of the naphthyridone ring.

In this study, we compared in vitro activity of CFC-222 with those of ciprofloxacin, ofloxacin, and lomefloxacin against several groups of clinical isolates. The effects of various assay conditions on the in vitro activity of CFC-222 were investigated. We also compared the in vivo protective efficacy of CFC-222 with those of the fluoroquinolones mentioned above against systemic models of infection in mice.

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MATERIALS AND METHODS

Antibacterial agents. CFC-222 and ciprofloxacin were synthesized at the Research and Development Center, Cheil Jedang Corporation (Ichon, Korea). Ofloxacin was obtained from Daiichi Pharmaceuticals (Tokyo, Japan), and lomefloxacin was obtained from Shionogi & Co. (Osaka, Japan).

Organisms. The reference strains used in this study were maintained in our laboratory, and clinical isolates were collected between 1990 and 1993 from several hospitals in Korea. All strains were stored frozen at −70°C until they were used.

Determination of MICs. MICs were determined by the twofold serial agar dilution method. The media used for preculture and MIC determinations were tryptic soy broth (Difco Laboratories, Detroit, Mich.) and Mueller-Hinton medium (Difco), respectively. The agar was supplemented with 10% horse serum for streptococci and 5% Fildes enrichment (Difco) for *Haemophilus influenzae*. Overnight cultures were diluted with buffered saline (pH 7.2) to a final cell density of 5×10^6 CFU/ml, and each bacterial suspension (inoculum size, 1×10^4 CFU/spot) was applied with a replicator (Cathra Systems, Columbus, Ohio) onto a series of Mueller-Hinton agar plates containing antibacterial agents. The plates were incubated for 18 h at 37°C. Activity against anaerobes was determined by the agar dilution method on GAM agar medium (Nissui Seiyaku, Tokyo, Japan) at 37°C for 48 h in anaerobic GasPak jars (BBL Microbiology

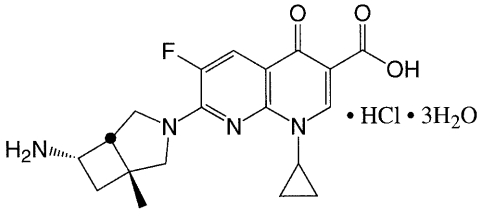

FIG. 1. Chemical structure of CFC-222.

TABLE 1. In vitro activities of CFC-222 against clinical isolates

Microorganism (no. of strains)[a]	Compound	MIC (μg/ml)			GM[b]
		Range	50%	90%	
MSSA (144)	CFC-222	0.05–0.39	0.10	0.20	0.11
	Ciprofloxacin	0.20–1.56	0.39	0.78	0.55
	Ofloxacin	0.20–0.78	0.39	0.39	0.38
	Lomefloxacin	0.78–6.25	1.56	1.56	1.39
MRSA (80)	CFC-222	0.05–25	0.10	6.25	0.32
	Ciprofloxacin	0.10–50	0.39	25	1.02
	Ofloxacin	0.10–12.5	0.20	6.25	0.53
	Lomefloxacin	0.78–>50	1.56	>50	3.56
QSSA (202)	CFC-222	0.05–0.39	0.10	0.20	0.10
	Ciprofloxacin	0.10–1.56	0.39	0.78	0.48
	Ofloxacin	0.10–0.78	0.39	0.39	0.33
	Lomefloxacin	0.78–6.25	1.56	1.56	1.35
QRSA (22)	CFC-222	0.05–25	6.25	12.5	6.67
	Ciprofloxacin	3.13–50	25	50	20.05
	Ofloxacin	0.39–>50	6.25	12.5	5.68
	Lomefloxacin	6.25–>50	50	>50	56.72
Staphylococcus epidermidis (17)	CFC-222	0.10–3.13	0.10	0.20	0.17
	Ciprofloxacin	0.10–6.25	0.20	0.39	0.34
	Ofloxacin	0.20–12.5	0.39	0.78	0.48
	Lomefloxacin	0.78–50	1.56	1.56	1.50
Streptococcus pyogenes (23)	CFC-222	0.20–0.78	0.39	0.78	0.37
	Ciprofloxacin	0.39–3.13	0.78	1.56	1.09
	Ofloxacin	0.78–6.25	3.13	3.13	2.24
	Lomefloxacin	3.13–50	25	25	15.44
Streptococcus pneumoniae (123)	CFC-222	0.05–0.39	0.20	0.20	0.20
	Ciprofloxacin	≤0.003–6.25	0.78	1.56	0.83
	Ofloxacin	0.39–3.13	1.56	3.13	1.79
	Lomefloxacin	1.56–25	12.5	12.5	9.92
Enterococcus faecalis (34)	CFC-222	0.20–0.78	0.39	0.39	0.37
	Ciprofloxacin	0.39–1.56	1.56	1.56	1.20
	Ofloxacin	1.56–6.25	3.13	6.25	3.40
	Lomefloxacin	6.25–25	12.5	12.5	9.59
Enterococcus faecium (24)	CFC-222	0.39–6.25	1.56	6.25	2.27
	Ciprofloxacin	0.78–12.5	3.13	12.5	4.42
	Ofloxacin	3.13–25	6.25	25	11.14
	Lomefloxacin	6.25–50	25	>50	29.73
Escherichia coli (90)	CFC-222	0.025–0.78	0.05	0.10	0.09
	Ciprofloxacin	≤0.003–0.20	0.012	0.025	0.02
	Ofloxacin	0.025–0.78	0.05	0.20	0.10
	Lomefloxacin	0.05–1.56	0.10	0.39	0.22
Klebsiella pneumoniae (70)	CFC-222	0.05–1.56	0.10	0.20	0.12
	Ciprofloxacin	0.006–0.39	0.05	0.05	0.05
	Ofloxacin	0.05–1.56	0.10	0.39	0.16
	Lomefloxacin	0.20–3.13	0.39	0.39	0.45
Enterobacter cloacae (70)	CFC-222	0.025–3.13	0.10	1.56	0.14
	Ciprofloxacin	≤0.003–0.39	0.025	0.39	0.04
	Ofloxacin	0.025–1.56	0.10	0.78	0.16
	Lomefloxacin	0.10–3.13	0.20	3.13	0.39
Enterobacter aerogenes (23)	CFC-222	0.05–0.10	0.10	0.10	0.08
	Ciprofloxacin	0.012–0.10	0.025	0.05	0.03
	Ofloxacin	0.05–0.20	0.10	0.10	0.10
	Lomefloxacin	0.20–0.39	0.20	0.39	0.24
Serratia marcescens (59)	CFC-222	0.05–>50	0.39	12.5	0.91
	Ciprofloxacin	0.025–>50	0.10	12.5	0.35
	Ofloxacin	0.012–25	0.39	12.5	0.74
	Lomefloxacin	0.012–50	0.39	25	0.74
Citrobacter freundii (27)	CFC-222	0.05–1.56	0.39	0.78	0.25
	Ciprofloxacin	0.006–0.39	0.05	0.20	0.06
	Ofloxacin	0.10–1.56	0.39	0.78	0.34
	Lomefloxacin	0.20–3.13	0.78	1.56	0.62
Morganella morganii (36)	CFC-222	0.10–0.39	0.10	0.39	0.20
	Ciprofloxacin	0.006–0.05	0.012	0.05	0.02
	Ofloxacin	0.025–0.20	0.10	0.20	0.13
	Lomefloxacin	0.10–0.39	0.10	0.39	0.21
Pseudomonas aeruginosa (146)	CFC-222	0.05–>50	3.13	25	5.32
	Ciprofloxacin	0.025–>50	0.39	25	1.28
	Ofloxacin	0.10–>50	1.56	>50	4.95
	Lomefloxacin	0.39–>50	3.13	>50	9.40
Acinetobacter baumannii (41)	CFC-222	0.10–3.13	0.20	0.78	0.36
	Ciprofloxacin	0.05–25	0.20	1.56	0.37
	Ofloxacin	0.10–12.5	0.20	0.78	0.39
	Lomefloxacin	0.39–50	0.78	6.25	1.46
Haemophilus influenzae (27)	CFC-222	0.012–0.39	0.025	0.20	0.05
	Ciprofloxacin	0.006–0.025	0.012	0.025	0.01
	Ofloxacin	0.025–0.20	0.05	0.10	0.06
	Lomefloxacin	0.05–0.39	0.20	0.20	0.16
Bacteroides fragilis (14)	CFC-222	1.56–6.25	3.13	6.25	2.69
	Ciprofloxacin	1.56–25	3.13	12.5	5.39
	Ofloxacin	0.78–12.5	3.13	3.13	2.56
	Lomefloxacin	6.25–50	12.5	25	13.80
Clostridium difficile (13)	CFC-222	0.39–>50	3.13	25	4.08
	Ciprofloxacin	1.56–>50	6.25	25	9.57
	Ofloxacin	1.56–>50	6.25	>50	9.07
	Lomefloxacin	6.25–>50	25	>50	30.94
Clostridium perfringens (6)	CFC-222	0.20–0.39	0.20		0.25
	Ciprofloxacin	0.39–0.39	0.39		0.39
	Ofloxacin	0.39–0.78	0.78		0.62
	Lomefloxacin	1.56–3.13	3.13		2.48

[a] MSSA, methicillin-susceptible *S. aureus* (methicillin MIC, ≤6.25 μg/ml); MRSA, methicillin-resistant *S. aureus* (methicillin MIC, ≤12.5 μg/ml); QSSA, ciprofloxacin-susceptible *S. aureus* (ciprofloxacin MIC, ≤1.56 μg/ml); QRSA, ciprofloxacin-resistant *S. aureus* (ciprofloxacin MIC, ≥3.13 μg/ml).

[b] GM, geometric mean, which is defined as the *n*th root of *n* variables multiplied by each other. MICs of >50 and ≤0.003 were regarded as 100 and 0.0015, respectively, to calculate the geometric mean.

Systems, Cockeysville, Md.). The cultures were diluted to a final cell density of 5×10^7 CFU/ml. The plates were inoculated with a replicator, which produced approximately 10^5 CFU/spot on the agar. Two plates of test medium without antibacterial agents were also incubated. One was incubated anaerobically to serve as a growth control, and the other was incubated aerobically to detect possible contamination with aerobes. The MIC was defined as the lowest antibacterial concentration that inhibited the development of visible microbial growth on agar. *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Bacteroides fragilis* ATCC 25285, obtained from the American Type Culture Collection (Rockville, Md.), were used as controls in the susceptibility tests.

Determination of MBCs. MICs for this study were determined by a twofold serial broth dilution method. Test strains, precultured overnight in tryptic soy broth (Difco), were inoculated at a final inoculum of approximately 5×10^5 CFU/ml into Mueller-Hinton broth (Difco) containing each compound. The MIC in liquid medium was defined as the lowest concentration of antibacterial agent that inhibited the development of visible bacterial growth after incubation for 18 h at 37°C. The minimal bactericidal concentration (MBC), defined as the lowest antibacterial concentration that killed ≥99.9% of the initial inoculum, was determined by subculturing 10 μl of the broth on antibiotic-free Mueller-Hinton agar (Difco), and after incubation for 24 h at 37°C, plates without visible growth were used to determine the MBC.

Effects of various conditions on in vitro activity. The effects of inoculum size, medium, pH, and serum on the antibacterial activity of CFC-222 against *S.*

TABLE 2. Bactericidal activity of CFC-222

Microorganism	CFC-222		Ciprofloxacin		Ofloxacin	
	MIC (μg/ml)[a]	MBC (μg/ml)[b]	MIC (μg/ml)	MBC (μg/ml)	MIC (μg/ml)	MBC (μg/ml)
Staphylococcus aureus Smith	0.05	0.10	0.20	0.39	0.20	0.39
Staphylococcus aureus ATCC 29213	0.10	0.20	0.39	0.78	0.39	0.39
Methicillin-resistant *Staphylococcus aureus* C5100	0.05	0.20	0.20	0.39	0.39	0.78
Staphylococcus epidermidis ATCC 12228	0.10	0.20	0.20	0.39	0.39	0.39
Escherichia coli C4002	0.05	0.05	0.012	0.05	0.20	0.20
Escherichia coli ATCC 25922	0.10	0.20	0.025	0.025	0.20	0.20
Enterobacter cloacae C4009	0.05	0.20	0.025	0.025	0.10	0.10
Klebsiella pneumoniae C1040	0.20	0.20	0.05	0.05	0.39	0.39
Proteus mirabilis ATCC 25933	12.5	25.0	0.05	0.05	0.10	0.20
Providencia rettgeri ATCC 9919	0.39	0.39	0.012	0.025	0.05	0.10
Salmonella typhimurium C4045	0.025	0.025	0.012	0.012	0.05	0.05
Serratia marcescens ATCC 271117	0.39	0.39	0.10	0.10	0.39	0.39
Pseudomonas aeruginosa GN11189	1.56	6.25	0.20	0.39	1.56	3.13
Pseudomonas aeruginosa ATCC 10145	1.56	3.13	0.20	0.39	1.56	1.56
Pseudomonas aeruginosa ATCC 27853	6.25	6.25	0.39	0.78	3.13	3.13

[a] Bacteriostatic activity.
[b] Bactericidal activity.

aureus Smith, *Staphylococcus epidermidis* ATCC 12228, *E. coli* C4002, *Enterobacter cloacae* C4008, *Klebsiella pneumoniae* C1040, *Serratia marcescens* C1052, and *P. aeruginosa* GN11189 were evaluated as described above for aerobic organisms.

(i) Media. The effect of medium on the MICs was determined with nutrient agar (Difco), Mueller-Hinton agar (Difco), heart infusion agar (Difco), brain heart infusion agar (Difco), and tryptic soy agar (Difco).

(ii) pH. The effect of pH on in vitro activity was determined with Mueller-Hinton agar (Difco) and an inoculum size of 10^6 CFU/ml. The medium pH was adjusted to 5.0, 6.0, 7.0, or 8.0 with 1 N NaOH or 1 N HCl prior to sterilization.

(iii) Serum. The effect of serum was evaluated with Mueller-Hinton agar (Difco) supplemented with heat-inactivated horse serum (Gibco BRL, Gaithersburg, Md.) to a final concentration of 10 or 25% (vol/vol).

(iv) Inoculum size. The effects of inoculum sizes from 10^6 to 10^9 CFU/ml on the antibacterial activity were determined with Mueller-Hinton medium (Difco).

Mouse protection tests. The organisms used in mouse protection tests were as follows: *S. aureus* Smith, *E. coli* C4002, *K. pneumoniae* C1040, and *P. aeruginosa* GN11189. The organisms were cultured overnight at 37°C in tryptic soy broth (Difco). Male ICR mice (weight, 20 to 25 g; age, 5 weeks; Charles River Japan, Yokohama, Kanagawa, Japan) were inoculated intraperitoneally with 0.3 ml of a bacterial suspension adjusted with 5% hog gastric mucin (ICN Biomedicals, Columbus, Ohio) in saline solution to 10 times the minimal lethal dose. The challenge inoculum was sufficient to kill 100% of the untreated control mice, which died within 48 h postinfection. Each test compound was administered once orally to mice immediately after infection with the exception of those inoculated with *P. aeruginosa*, which were treated twice (immediately and 1 h postinfection). Five groups of eight mice each were treated with different doses of each antibacterial agent. The median protective dose was calculated by the method of Litchfield and Wilcoxon (11) from the survival rates on day 7 after infection.

RESULTS

In vitro antibacterial activity. The in vitro antibacterial activities of CFC-222 and the other quinolone agents tested against several groups among clinical isolates are presented in Table 1. CFC-222 was the most active of the compounds tested against gram-positive bacteria. CFC-222 was fourfold more active than ciprofloxacin against quinolone-susceptible *S. aureus* (MICs at which 90% of isolates are inhibited [MIC_{90}s], 0.2 and 0.78 μg/ml, respectively) and also fourfold more active than ciprofloxacin against quinolone-resistant *S. aureus* (MIC_{90}s, 12.5 and 50 μg/ml, respectively). CFC-222 showed activity similar to that of ofloxacin against both ciprofloxacin-susceptible and -resistant *S. aureus* strains. CFC-222 was the most active compound tested against streptococci. CFC-222 was 8-fold more active than ciprofloxacin and 16-fold more active than ofloxacin (MIC_{90}s, 0.2, 1.56, and 3.13 μg/ml, respectively). CFC-222 showed activity superior to those of the other quinolones tested against enterococci. CFC-222 was fourfold more active than ciprofloxacin against *E. faecalis* (MIC_{90}s, 0.39 and 1.56 μg/ml, respectively), but it was less active against *Enterococcus faecium* (MIC_{90}s, 6.25 μg/ml for CFC-222 and 12.5 μg/ml for ciprofloxacin).

Against gram-negative bacteria, including members of the family *Enterobacteriaceae*, *P. aeruginosa*, *Acinetobacter baumannii*, and *H. influenzae*, CFC-222 was less active than ciprofloxacin, but it was as active as ofloxacin. Against anaerobes, CFC-222 was twofold more active than ciprofloxacin in terms of its geometric mean activity.

Effects of various conditions on in vitro activity. The activities of CFC-222 and the other quinolones tested, determined with bacteria grown on nutrient agar, heart infusion agar, brain heart infusion agar, and tryptic soy agar, were nearly equal to those determined in Mueller-Hinton agar (data not shown). A difference in the medium pH of between 7 and 8 did not affect the activity of CFC-222 against each organism. However, the activity of CFC-222 at pH 5 and 6 significantly decreased by 4- to 16-fold, as did those of the other quinolones tested (data not shown). Serum contents of 0, 10, and 25% had no significant effect on the activities of CFC-222 and the other quinolones tested (data not shown). An increase in the inoculum size from 10^6 to 10^9 CFU/ml had no significant effect on the in vitro activity of CFC-222 against each organism (data not shown).

Bactericidal activity. The bactericidal activity of CFC-222 against 12 standard strains is presented in Table 2. The MBCs of CFC-222 for the strains tested were either equal to or twofold higher than the MICs, as were observed for the other fluoroquinolones. Accordingly, CFC-222 and the fluoroquinolones studied had bactericidal activity.

Mouse protection tests. The therapeutic efficacy of CFC-222 against experimental systemic infections with gram-positive cocci and gram-negative organisms in mice is presented in Table 3. Against *S. aureus* Smith, CFC-222 was approximately twofold more effective than ciprofloxacin or ofloxacin, whose effects were not significantly different from one another.

CFC-222 exhibited efficacy either equal to or comparable to that of ciprofloxacin against *E. coli* C4002 and *K. pneumoniae* C1040, respectively, although the MICs of CFC-222 were fourfold weaker than those of ciprofloxacin. Against *P. aeruginosa*

TABLE 3. Protective effects of CFC-222 on systemic infections in mice

Microorganism	Challenge dose (CFU/mouse)	Compound[a]	MIC (μg/ml)	PD_{50} (mg/kg)[b]	95% Confidence limits
S. aureus Smith	8.7×10^6	CFC-222	0.10	0.40	0.23–0.65
		Ciprofloxacin	0.20	2.33	1.36–4.27
		Ofloxacin	0.39	2.08	1.27–3.41
		Lomefloxacin	0.78	4.64	2.99–6.91
E. coli C4002	1.4×10^6	CFC-222	0.20	0.71	0.47–1.04
		Ciprofloxacin	0.05	0.65	0.45–0.93
		Ofloxacin	0.10	1.37	0.92–2.00
		Lomefloxacin	0.39	1.67	1.15–2.35
K. pneumoniae C1040	1.5×10^6	CFC-222	0.20	0.59	0.26–0.99
		Ciprofloxacin	0.05	0.34	0.20–0.52
		Ofloxacin	0.20	1.23	0.67–1.93
		Lomefloxacin	0.39	1.02	0.71–1.46
P. aeruginosa GN11189	5.7×10^5	CFC-222	3.13	2.17	1.27–3.83
		Ciprofloxacin	0.39	0.74	0.44–1.17
		Ofloxacin	1.56	3.65	2.57–5.21
		Lomefloxacin	3.13	4.00	2.75–5.82

[a] Each test compound was administered once orally to mice immediately postinfection with the exception of those inoculated with *P. aeruginosa*, which were treated twice (immediately and 1 h postinfection).

[b] The number of survivors on day 7 postinfection was used to calculate the median protective dose (PD_{50}) by the Litchfield-Wilcoxon method (95% confidence limits) ($P < 0.05$).

GN11189, CFC-222 was slightly less active than ciprofloxacin but was as active as ofloxacin.

DISCUSSION

CFC-222 demonstrated potent in vitro antibacterial activity against a broad spectrum of organisms, and its activity was comparable to those of other quinolones currently used to treat infectious diseases caused by these pathogens. In particular, the improved antibacterial efficacy of CFC-222 against pneumococci was the most prominent difference. CFC-222 showed more potent activity than the other quinolones tested against other gram-positive organisms, including *S. aureus*, *S. epidermidis*, *Streptococcus pyogenes*, and *E. faecalis.* The clinical usefulness of CFC-222 against *E. faecium* needs to be evaluated in future studies. The activity of CFC-222 against gram-negative organisms was comparable to that of ciprofloxacin.

Although the activity of CFC-222 was not affected by test conditions such as medium, inoculum size, or horse serum content, it was decreased by a change in the pH to 6.0, as were those of the other quinolones tested (3, 12). The mode of antibacterial action of CFC-222 was typically bactericidal. MBCs were not substantially different from MICs for gram-positive and gram-negative organisms, as was the case for the other quinolones tested (2, 12, 15).

The in vivo efficacy of CFC-222 against a gram-positive bacterium, *S. aureus* Smith, was superior to those of ciprofloxacin and ofloxacin. The protective activity against gram-negative organisms, such as *E. coli* and *K. pneumoniae*, was comparable to that of ciprofloxacin, even though the MICs of CFC-222 were four times weaker than those of ciprofloxacin.

Phamacokinetic studies with mice without infection indicated that after administration of a single oral dose of 20 mg/kg, CFC-222 was absorbed rapidly; its maximum concentration in serum was 4.9 μg/ml (6). Its half-life in serum was 6 h, whereas that of ciprofloxacin was 1.6 h (data not shown). These features of CFC-222 probably reflect the excellent in vivo efficacy in mice.

The fluoroquinolones have proven to be a very useful therapeutic class of agents for the treatment of infectious diseases, including those of the respiratory tract, urinary tract, and skin and soft tissues, as well as sexually transmitted diseases. Recent concerns with the limited activities of fluoroquinolones against gram-positive organisms, particularly streptococci (2, 16) and staphylococci (2, 5, 14), have pointed to the need to develop compounds with improved activity against *S. pneumoniae* and *S. aureus.*

CFC-222 showed excellent in vitro and in vivo activities against gram-positive bacteria, including streptococci and staphylococci, and in vitro and in vivo efficacies comparable to those of ciprofloxacin against gram-negative organisms (7–10). CFC-222 also had superior pharmacokinetic characteristics (6). Despite its excellent in vivo activities and superior pharmacokinetic profiles, the clinical usefulness of CFC-222 should be established by further studies. Phase I studies of CFC-222 have been completed, and phase II studies are planned.

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