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In Vitro Antibacterial Activity of ME1207, a New Oral Cephalosporin

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ME1207 is the prodrug of ME1206. Its in vitro antibacterial activity was compared with that of cefteram, cefpodoxime, cefixime, and cefaclor against various clinical isolates. ME1206 was more active than the other cephems tested against staphylococci, streptococci, *Morganella morganii*, *Pseudomonas cepacia*, and *Flavobacterium meningosepticum* and had the most potent activity against *Haemophilus influenzae* and *Neiserria gonorrhoeae*. The drug also showed a wide spectrum of activity against other gram-positive and gram-negative bacteria, except methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Xanthomonas maltophilia*, and *Alcaligenes xylosoxydans*.

ME1207 is a new oral cephalosporin prodrug which is de-esterified in the intestine to its active form (ME1206) (Fig. 1). ME1206 was previously shown to possess a wide spectrum of bacterial activity and is undergoing extensive clinical evaluation in Japan (3). However, studies to date have not demonstrated the full range of activity of ME1206, especially that against the various pathogens which are the targets of chemotherapy in compromised hosts. In this study, we compared the in vitro activities of ME1206 and those of newly developed oral cephalosporins against a wide range of fresh clinical isolates, including methicillin-resistant *Staphylococcus aureus* and various opportunistic pathogens. All strains tested were isolated from specimens from patients at various hospitals in Japan. The sodium salt of ME1206 was synthesized at the Pharmaceutical Research Laboratories, Meiji Seika Kaisha, Ltd., Yokohama, Japan. The other drugs were obtained as follows: cefteram, Toyama Chemical Co., Ltd., Tokyo, Japan; cefpodoxime, Sankyo Co., Ltd., Tokyo, Japan; cefixime, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan; cefaclor, Shionogi Pharmaceutical Co., Ltd., Osaka, Japan.

MICs were determined by the agar dilution method according to the reference procedure recommended by the Japan Society for Chemotherapy (2). Mueller-Hinton agar (Difco Laboratories, Detroit, Mich.) was used for the tested medium, unless otherwise specified (2). When streptococci were tested, brain heart infusion agar was supplemented with 5% defibrinated horse blood. For *Haemophilus influenzae*, Mueller-Hinton agar was supplemented with 10% defibrinated horse blood and 1% glycerin (Wako Pure Chemical Co., Ltd., Osaka, Japan). For *Neisseria gonorrhoeae*, GC medium base (Difco) was supplemented with a 2% solution containing carboxylase (Wako) (0.001 g) and glucose (Wako) (0.5 g) in 100 ml of distilled water. All inocula were from 24-h broth growths. The final inoculum was 10^4 CFU per spot, and results were noted after overnight incubation at 37°C in an aerobic atmosphere, except for *Haemophilus* and *Neisseria* species, which were incubated in 5% CO_2. For anaerobic bacteria, GAM broth (Nissui Seiyaku Co., Ltd., Tokyo, Japan) was used for preculture and MIC determination (1). Incubation was carried out for 48 h in an anaerobic chamber.

The MICs for 50 and 90% of isolates tested (MIC_{50} and MIC_{90}) and the range of MICs of the five cephems for 32 species are shown in Table 1. ME1206 was more active than the other cephems tested against methicillin-susceptible *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* but like the other cephems was inactive against methicillin-resistant *Staphylococcus aureus* and *En-*

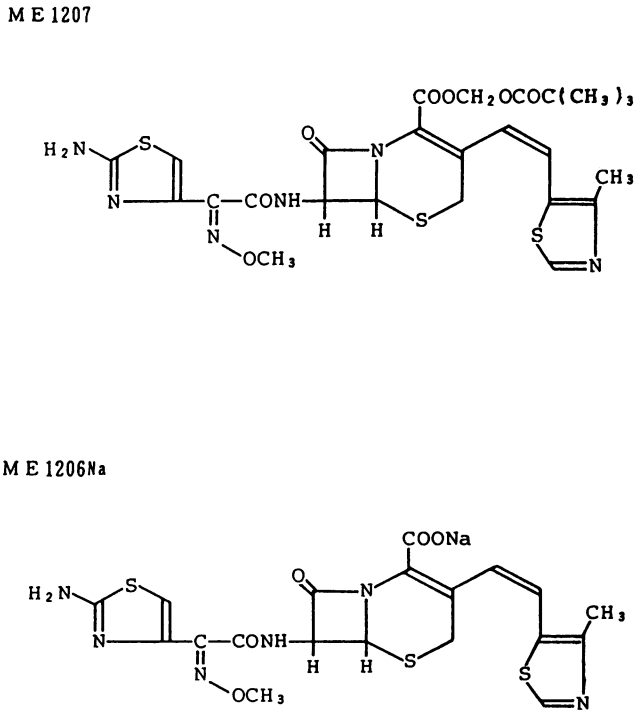

FIG. 1. Structure of ME1207 and ME1026 (ME1206Na).

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TABLE 1. In vitro antibacterial activity against clinical isolates

Organism[a] (no. of strains)	Antibiotic	MIC (μg/ml)[b]		
		Range	50%	90%
Staphylococcus aureus (MS) (62)	ME1206	0.10–12.5	0.78	3.13
	Cefpodoxime	0.39–>100	3.13	25
	Cefteram	0.39–100	3.13	25
	Cefixime	0.78–>100	12.5	100
	Cefaclor	0.39–100	3.13	50
Staphylococcus aureus (MR) (48)	ME1206	6.25–>100	25	100
	Cefpodoxime	25–>100	>100	>100
	Cefteram	25–>100	>100	>100
	Cefixime	50–>100	>100	>100
	Cefaclor	50–>100	>100	>100
Staphylococcus epidermidis (MS) (45)	ME1206	0.10–6.25	0.20	0.39
	Cefpodoxime	0.20–6.25	0.78	1.56
	Cefteram	0.20–6.25	1.56	6.25
	Cefixime	1.56–50	6.25	12.5
	Cefaclor	0.78–12.5	1.56	1.56
Streptococcus pyogenes (49)	ME1206	≤0.006–0.012	≤0.006	≤0.006
	Cefpodoxime	≤0.006–0.025	0.012	0.025
	Cefteram	≤0.006–0.012	≤0.006	0.012
	Cefixime	0.10–0.20	0.10	0.10
	Cefaclor	0.20–0.39	0.20	0.20
Streptococcus agalactiae (40)	ME1206	0.012–0.025	0.025	0.025
	Cefpodoxime	0.05–0.10	0.05	0.05
	Cefteram	0.025–0.05	0.05	0.05
	Cefixime	0.39–0.78	0.39	0.39
	Cefaclor	1.56–3.13	1.56	3.13
Streptococcus pneumoniae (PS) (42)	ME1206	≤0.006–1.56	0.012	0.78
	Cefpodoxime	0.025–12.5	0.05	3.13
	Cefteram	0.012–6.25	0.025	3.13
	Cefixime	0.20–100	0.39	25
	Cefaclor	0.78–>100	1.56	>100
Enterococcus faecalis (30)	ME1206	0.20–>100	>100	>100
	Cefpodoxime	1.56–>100	>100	>100
	Cefteram	0.78–>100	>100	>100
	Cefixime	0.78–>100	>100	>100
	Cefaclor	50–100	100	100
Escherichia coli (50)	ME1206	0.012–0.39	0.10	0.20
	Cefpodoxime	0.05–1.56	0.39	0.78
	Cefteram	≤0.006–0.39	0.20	0.39
	Cefixime	0.025–0.78	0.20	0.39
	Cefaclor	0.20–12.5	3.13	6.25
Shigella sp. (30)	ME1206	0.025–0.39	0.10	0.20
	Cefpodoxime	0.05–0.78	0.39	0.39
	Cefteram	0.025–0.39	0.10	0.39
	Cefixime	≤0.006–0.78	0.39	0.78
	Cefaclor	0.39–3.13	1.56	3.13
Salmonella sp. (30)	ME1206	0.10–0.78	0.20	0.78
	Cefpodoxime	0.10–3.13	0.39	1.56
	Cefteram	0.10–1.56	0.20	1.56
	Cefixime	≤0.006–0.39	0.05	0.20
	Cefaclor	0.012–3.13	0.78	3.13
Citrobacter freundii (29)	ME1206	0.10–>100	25	100
	Cefpodoxime	0.78–>100	>100	>100
	Cefteram	0.20–>100	50	>100
	Cefixime	0.20–>100	100	>100
	Cefaclor	6.25–>100	>100	>100
Klebsiella pneumoniae (40)	ME1206	0.012–0.39	0.10	0.20
	Cefpodoxime	≤0.006–0.78	0.10	0.20
	Cefteram	≤0.006–0.78	0.10	0.20
	Cefixime	≤0.006–0.20	0.05	0.05
	Cefaclor	≤0.006–25	0.78	3.13
Klebsiella oxytoca (30)	ME1206	0.05–0.78	0.10	0.20
	Cefpodoxime	0.05–3.13	0.10	0.78
	Cefteram	0.05–3.13	0.10	0.39
	Cefixime	≤0.006–3.13	0.012	0.05
	Cefaclor	0.78–>100	1.56	50

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TABLE 1—*Continued*

Organism[a] (no. of strains)	Antibiotic	MIC (μg/ml)[b]		
		Range	50%	90%
Enterobacter cloacae (31)	ME1206	0.025–100	3.13	50
	Cefpodoxime	0.20–>100	12.5	>100
	Cefteram	0.025–100	6.25	100
	Cefixime	≤0.006–>100	3.13	100
	Cefaclor	0.39–>100	>100	>100
Serratia marcescens (40)	ME1206	0.39–25	0.78	3.13
	Cefpodoxime	0.20–100	0.78	3.13
	Cefteram	≤0.006–50	0.78	3.13
	Cefixime	0.10–25	0.20	0.78
	Cefaclor	25–>100	>100	>100
Proteus vulgaris (31)	ME1206	≤0.006–1.56	0.10	0.39
	Cefpodoxime	≤0.006–12.5	0.20	1.56
	Cefteram	≤0.006–6.25	0.05	0.39
	Cefixime	≤0.006–0.78	0.012	0.025
	Cefaclor	1.56–>100	>100	>100
Proteus mirabilis (26)	ME1206	0.05–0.20	0.05	0.20
	Cefpodoxime	0.05–0.20	0.05	0.20
	Cefteram	0.025–0.10	0.05	0.10
	Cefixime	≤0.006–0.012	0.012	0.012
	Cefaclor	0.10–>100	1.56	6.25
Providencia stuartii (27)	ME1206	0.10–12.5	0.39	1.56
	Cefpodoxime	0.012–3.13	0.05	0.78
	Cefteram	0.025–12.5	0.20	3.13
	Cefixime	≤0.006–0.78	0.012	0.10
	Cefaclor	3.13–>100	12.5	>100
Providencia rettgeri (30)	ME1206	≤0.006–6.25	0.05	1.56
	Cefpodoxime	≤0.006–6.25	0.012	0.78
	Cefteram	≤0.006–12.5	0.025	1.56
	Cefixime	≤0.006–0.78	≤0.006	0.10
	Cefaclor	0.78–>100	50	>100
Morganella morganii (33)	ME1206	≤0.006–12.5	0.10	12.5
	Cefpodoxime	≤0.006–100	0.78	100
	Cefteram	≤0.006–25	0.10	25
	Cefixime	≤0.006–50	0.78	25
	Cefaclor	0.78–>100	>100	>100
Pseudomonas aeruginosa (35)	ME1206	12.5–>100	50	>100
	Cefpodoxime	>100–>100	>100	>100
	Cefteram	50–>100	>100	>100
	Cefixime	25–>100	100	>100
	Cefaclor	>100–>100	>100	>100
Pseudomonas cepacia (17)	ME1206	0.10–50	3.13	12.5
	Cefpodoxime	0.20–>100	1.56	50
	Cefteram	0.20–>100	6.25	25
	Cefixime	0.20–>100	1.56	50
	Cefaclor	3.13–>100	50	>100
Xanthomonas maltophilia (28)	ME1206	12.5–>100	50	>100
	Cefpodoxime	100–>100	>100	>100
	Cefteram	50–>100	>100	>100
	Cefixime	12.5–>100	>100	>100
	Cefaclor	>100–>100	>100	>100
Acinetobacter calcoaceticus (20)	ME1206	0.012–25	6.25	12.5
	Cefpodoxime	0.012–12.5	1.56	6.25
	Cefteram	0.025–25	6.25	12.5
	Cefixime	0.05–50	3.13	12.5
	Cefaclor	0.05–>100	50	100
Flavobacterium meningosepticum (21)	ME1206	0.78–12.5	3.13	6.25
	Cefpodoxime	0.39–>100	12.5	50
	Cefteram	0.78–50	12.5	50
	Cefixime	6.25–>100	50	100
	Cefaclor	25–>100	100	>100
Alcaligenes xylosoxidans (17)	ME1206	0.10–>100	50	>100
	Cefpodoxime	3.13–>100	>100	>100
	Cefteram	0.78–>100	100	>100
	Cefixime	1.56–>100	25	>100
	Cefaclor	1.56–>100	50	>100

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TABLE 1—*Continued*

Organism[a] (no. of strains)	Antibiotic	MIC (μg/ml)[b]		
		Range	50%	90%
Bordetella pertussis (21)	ME1206	3.13–25	12.5	25
	Cefpodoxime	12.5–25	12.5	12.5
	Cefteram	1.56–50	3.13	50
	Cefixime	1.56–3.13	1.56	3.13
	Cefaclor	3.13–50	25	50
Haemophilus influenzae (BN) (27)	ME1206	≤0.006–0.025	0.012	0.025
	Cefpodoxime	0.012–0.10	0.10	0.10
	Cefteram	≤0.006–0.025	0.025	0.025
	Cefixime	≤0.006–0.05	0.025	0.05
	Cefaclor	0.20–6.25	1.56	3.13
Neisseria gonorrhoeae (Non-PP) (35)	ME1206	≤0.006–0.012	≤0.006	≤0.006
	Cefpodoxime	≤0.006–0.025	≤0.006	0.012
	Cefteram	≤0.006–0.025	≤0.006	0.025
	Cefixime	≤0.006–0.012	≤0.006	≤0.006
	Cefaclor	≤0.006–1.56	0.39	0.78
Neisseria gonorrhoeae (PP) (33)	ME1206	≤0.006–0.012	≤0.006	≤0.006
	Cefpodoxime	≤0.006–0.012	≤0.006	0.012
	Cefteram	≤0.006–0.05	0.012	0.025
	Cefixime	≤0.006–≤0.006	≤0.006	≤0.006
	Cefaclor	≤0.006–0.78	0.39	0.78
Bacteroides fragilis (29)	ME1206	0.78–6.25	3.13	6.25
	Cefpodoxime	100–>100	100	>100
	Cefteram	12.5–100	50	50
	Cefixime	100–>100	100	>100
	Cefaclor	>100–>100	>100	>100
Clostridium difficile (19)	ME1206	3.13–25	12.5	25
	Cefpodoxime	100–100	100	100
	Cefteram	25–50	50	50
	Cefixime	>100–>100	>100	>100
	Cefaclor	12.5–25	12.5	25

[a] Inoculum size; 10^6 cells per ml. MS, methicillin susceptible; MR, methicillin resistant; PS, penicillin susceptible; BN, β-lactamase negative; PP, penicillinase-producing.
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.

terococcus faecalis. The activity of ME1206 against members of the family *Enterobacteriaceae* was varied by species. At 0.2 to 0.39 μg/ml, ME1206 inhibited 90% of *Escherichia coli*, *Shigella* spp., *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus vulgaris*, and *Proteus mirabilis* strains with an activity greater than that of cefpodoxime, cefteram, and cefaclor. For *Serratia marcescens*, *Salmonella* spp., *Providencia stuartii*, and *Providencia rettgeri*, the MIC_{90} of ME1206 was less than or equal to 3.13 μg/ml, and its activities were very similar to those of cefpodoxime and cefteram but were greater than those of cefaclor. ME1206 had the most potent activity against *Haemophilus influenzae* and *Neisseria gonorrhoeae*, including β-lactamase-producing strains of these species (MIC_{90}s, ≤0.006 to 0.25 μg/ml), similar to cefixime. ME1206 was more active than the other cephems tested against *Morganella morganii*, *Pseudomonas cepacia*, and *Flavobacterium meningosepticum*, with MIC_{90}s equal to or less than 12.5 μg/ml, but was appreciably less active than cefixime against *Bordetella pertussis* (MIC_{90}, 25 μg/ml) and also against *Acinetobacter calcoaceticus* (MIC_{90}, 12.5 μg/ml). Like the other cephems, ME1206 failed to inhibit *Citrobacter freundii*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Xanthomonas maltophilia*, and *Alcaligenes xylosoxydans*. ME1206 was the most active drug tested against *Bacteroides fragilis* with a MIC_{90} of 6.25 μg/ml. For *Clostridium difficile*, ME1206 had MICs that ranged from 3.13 to 25 μg/ml, with a MIC_{90} of 25 μg/ml.

We believe that these findings suggest the clinical potential of ME1207 (ME1206) and that the drug merits investigation at the patient level.

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