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In Vitro and In Vivo Antibacterial Activities of ME1207, a New Oral Cephalosporin

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ME1207 (pivaloyloxymethyl ester of ME1206) is a new oral cephalosporin. ME1206 is (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)-acetamido]-3-[(*Z*)-2-(4-methylthiazol-5-yl)-ethenyl]-cephem-4-carboxylic acid. The susceptibilities of about 1,600 clinical isolates to ME1206 were determined by the agar dilution method. ME1206 showed a broad spectrum of activity against gram-positive and gram-negative bacteria. ME1206 was more active than cefaclor, T-2525, and cefixime against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Against gram-negative bacteria, the activity of ME1206 was comparable with that of T-2525, but ME1206 was less active than cefixime. Against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*, ME1206 had high activity (MIC, ≤0.05 μg/ml). ME1206 was stable against various β-lactamases, except β-lactamases from *Providencia rettgeri*, *Pseudomonas cepacia*, and *Escherichia coli* W3630 (Rms213). The 50% effective doses of ME1207 after oral administration against systemic infections in mice were comparable with those of T-2588 against gram-negative bacteria and about one-fourth that of T-2588 against *Staphylococcus aureus* Smith.

Recently there has been great progress in the development of oral cephalosporins, but those oral cephalosporins still have defects to overcome. Cefaclor is active against gram-positive and gram-negative bacteria but not stable against various β-lactamases (1, 12). Cefixime has strong activity against gram-negative bacteria and is highly stable against various β-lactamases, but cefixime has poor activity against staphylococci (5). T-2525 (cefterame) is the biologically active product of the orally administered prodrug (T-2588). T-2525 is active against gram-negative bacteria and *Streptococcus pneumoniae*, but is less active than cefaclor against staphylococci (2, 11, 13). R-3746 is the biologically active product of CS-807. R-3746 is active against gram-negative bacteria, and its activity against staphylococci is equal to cefaclor (18).

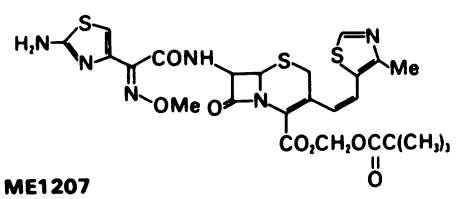
ME1206 has high activity against gram-positive bacteria in addition to gram-negative bacteria (M. Inoue, A. Tamura, T. Yoshida, R. Okamoto, K. Atsumi, K. Nishihata, and S. Mitsuhashi, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 582, 1985). This paper summarizes our observations on the in vitro and in vivo activities of this new oral cephalosporin and its stability against β-lactamases.

MATERIALS AND METHODS

Compounds. ME1206 (sodium salt) and ME1207 (Fig. 1) were synthesized at Pharmaceutical Research Laboratories, Meiji Seika Kaisha, Ltd., Yokohama, Japan. The other compounds were obtained as follows: T-2525 and T-2588, Toyama Chemical Co., Ltd., Tokyo, Japan; cefixime, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan; cefaclor, Shionogi Pharmaceutical Co., Ltd., Osaka, Japan; cephaloridine, Nippon Glaxo Co., Ltd., Tokyo, Japan; and benzylpenicillin, Meiji Seika Kaisha, Ltd., Tokyo, Japan.

Organisms. Recent clinical isolates were collected from various laboratories and hospitals and maintained in the Laboratory of Drug Resistance in Bacteria, School of Medicine, Gunma University, Gunma, Japan, and in the Episome Institute, Gunma, Japan.

Determinations of MICs. MICs were determined by the twofold agar dilution method with sensitivity disk agar (Nissui Seiyaku Co., Ltd., Tokyo, Japan), unless otherwise specified. For *Streptococcus* spp., sensitivity disk agar was supplemented with 5% defibrinated horse blood. For *Haemophilus influenzae*, sensitivity disk agar was supplemented with 5% Bacto Fildes Enrichment (Difco Laboratories, Detroit, Mich.). The organisms were grown overnight in sensitivity test broth (STB) (Nissui Seiyaku) at 37°C. STB containing 0.4% potassium nitrate was used for the culture of *Pseudomonas* spp. STB containing 5% Bacto Fildes Enrichment was used for the culture of *Haemophilus influenzae*. The culture was diluted with buffered saline containing gelatin to a final concentration of 10^6 CFU/ml, and a final inoculum of 10^4 CFU per spot was applied to agar



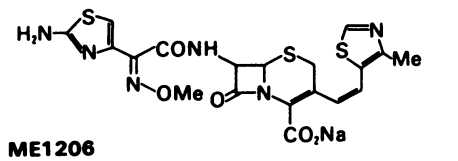


FIG. 1. Chemical structures of ME1207 (pivaloyloxymethyl ester of ME1206) and ME1206.

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TABLE 1. Antibacterial activity of ME1206 and three other antibiotics against clinical isolates

Organism (no. of isolates)	Compound	MIC (μg/ml)		
		Range	50%	90%
Methicillin-susceptible *Staphylococcus aureus* (66)	ME1206	0.39–0.78	0.78	0.78
	T-2525	1.56–6.25	3.13	3.13
	Cefixime	6.25–25	12.5	12.5
	Cefaclor	1.56–6.25	1.56	3.13
Staphylococcus epidermidis (100)	ME1206	0.05–100	0.78	6.25
	T-2525	0.20–>100	3.13	25
	Cefixime	0.78–>100	12.5	100
	Cefaclor	≤0.025–>100	1.56	12.5
Streptococcus pneumoniae (22)	ME1206	≤0.025	≤0.025	≤0.025
	T-2525	≤0.025	≤0.025	≤0.025
	Cefixime	0.05–0.20	0.10	0.20
	Cefaclor	0.20–0.39	0.39	0.39
Streptococcus pyogenes (91)	ME1206	≤0.025	≤0.025	≤0.025
	T-2525	≤0.025	≤0.025	≤0.025
	Cefixime	≤0.025–0.20	0.05	0.10
	Cefaclor	0.05–0.39	0.10	0.20
Escherichia coli (95)	ME1206	≤0.025–0.78	0.20	0.39
	T-2525	≤0.025–0.78	0.20	0.39
	Cefixime	≤0.025–1.56	0.20	0.39
	Cefaclor	0.39–6.25	1.56	3.13
Citrobacter freundii (76)	ME1206	0.10–100	0.78	25
	T-2525	0.10–>100	0.78	100
	Cefixime	0.10–>100	0.78	>100
	Cefaclor	0.39–>100	12.5	>100
Klebsiella pneumoniae (44)	ME1206	0.10–3.13	0.39	0.39
	T-2525	0.10–1.56	0.20	0.20
	Cefixime	≤0.025–0.20	≤0.025	0.05
	Cefaclor	0.20–6.25	0.78	1.56
Klebsiella oxytoca (51)	ME1206	0.05–1.56	0.20	0.39
	T-2525	≤0.025–1.56	0.10	0.39
	Cefixime	≤0.025–0.05	≤0.025	≤0.025
	Cefaclor	0.39–50	0.78	12.5
Salmonella spp. (105)	ME1206	0.20–0.78	0.39	0.39
	T-2525	0.20–0.78	0.39	0.39
	Cefixime	0.05–0.20	0.10	0.10
	Cefaclor	0.39–1.56	0.78	0.78
Proteus mirabilis (98)	ME1206	0.05–0.39	0.10	0.20
	T-2525	≤0.025–0.20	0.05	0.10
	Cefixime	≤0.025	≤0.025	≤0.025
	Cefaclor	0.39–3.13	1.56	1.56
Proteus vulgaris (78)	ME1206	≤0.025–6.25	0.10	0.39
	T-2525	≤0.025–12.5	0.10	0.39
	Cefixime	≤0.025–0.39	≤0.025	≤0.025
Providencia rettgeri (53)	ME1206	≤0.025–6.25	0.20	0.78
	T-2525	≤0.025–12.5	0.05	0.39
	Cefixime	≤0.025–1.56	≤0.025	0.05
Morganella morganii (89)	ME1206	≤0.025–25	0.20	0.78
	T-2525	≤0.025–50	0.10	0.39
	Cefixime	≤0.025–>100	0.10	3.13
Serratia marcescens (108)	ME1206	0.10–50	0.78	6.25
	T-2525	≤0.025–100	1.56	12.5
	Cefixime	≤0.025–100	0.20	3.13

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TABLE 1—*Continued*

Organism (no. of isolates)	Compound	MIC (μg/ml)		
		Range	50%	90%
Enterobacter cloacae (100)	ME1206	0.10–>100	0.78	50
	T-2525	0.05–>100	1.56	100
	Cefixime	0.05–>100	3.13	>100
Pseudomonas cepacia (51)	ME1206	0.20–100	3.13	6.25
	T-2525	0.78–>100	3.13	12.5
	Cefixime	≤0.025–100	0.78	1.56
	Cefaclor	1.56–>100	>100	>100
Haemophilus influenzae (47)	ME1206	≤0.025	≤0.025	≤0.025
	T-2525	≤0.025	≤0.025	≤0.025
	Cefixime	≤0.025	≤0.025	≤0.025
	Cefaclor	0.78–6.25	1.56	6.25
Neisseria gonorrhoeae (17)	ME1206	≤0.025–0.05	≤0.025	0.05
	T-2525	≤0.025–0.05	≤0.025	0.05
	Cefixime	≤0.025	≤0.025	≤0.025
	Cefaclor	0.10–3.13	0.78	1.56
Bacteroides fragilis (27)	ME1206	0.78–100	3.13	100
	T-2525	0.78–>100	12.5	>100
	Cefixime	0.20–>100	12.5	>100
	Cefaclor	25–>100	50	>100

plates with an inoculator (Microplanter; Sakuma Seisakusho, Tokyo, Japan). Inoculated plates were incubated for 18 h at 37°C. For *Neisseria gonorrhoeae*, Proteose No. 3 Agar (Difco) was supplemented with 0.2 g of hemoglobin (Difco) and 0.01 ml of IsoVitaleX Enrichment (BBL Microbiology Systems, Cockeysville, Md.) per ml. The bacterial suspension of *N. gonorrhoeae* was prepared directly from the overnight agar plate culture, and inoculated plates were incubated in a candle extinction jar. For *Bacteroides fragilis*, GAM broth and GAM agar (Nissui Seiyaku) were used and *B. fragilis* was cultured in an anaerobic glove box. The MIC was defined as the lowest concentration of the compound that prevented visible growth.

Bactericidal activity. The MICs and MBCs were determined by the twofold broth dilution method. Tubes (1 ml) containing serial twofold dilutions of the compounds in STB were inoculated with overnight cultures in STB at 37°C to yield a final inoculum of about 5×10^5 CFU/ml. Tubes were incubated for 18 h at 37°C. The MIC was defined as the lowest concentration of the compound that prevented visible growth in broth. The MBC was determined by subculture of 0.05 ml of broth in tubes without visible growth and was defined as the concentration which produced ≧99.9% reduction in CFU after 18 h of incubation at 37°C.

Stability against β-lactamases. The various types of β-lactamases (10, 14) used were totally or partially purified enzymes (3, 4, 6, 7, 9, 16). The stability of various β-lactamases was determined by spectrophotometric assay by measuring the absorbance at the absorption maximum of each compound (19). The molecular absorbancy difference ($\Delta\varepsilon$) and the specific wavelength for ME1206 were 2.40/mM per cm and 274 nm, respectively. The relative rate of hydrolysis was determined as the initial rate at 100 μM of each compound.

Assay of PBPs. Preparation of membrane fractions was performed by the method of Utsui and Yokota (17). The membrane suspension was adjusted to a concentration of 8 mg of protein per ml. Penicillin-binding proteins (PBPs) were assayed by the method of Spratt (15) with some modification. Experiments to determine the binding affinity of ME1206 for PBPs were performed by preincubation of the membrane fractions with ME1206 at 30°C for 10 min before addition of ^{14}C-labeled penicillin G (Amersham Corp., Arlington Heights, Ill.; specific activity, 54 mCi/mmol). Fluorographs of PBPs were analyzed quantitatively with a densitometer, and the I_{50} (concentration required to inhibit ^{14}C-labeled penicillin G binding by 50%) was calculated.

Determination of in vivo activity. The in vivo antibacterial

TABLE 2. Correlation between MIC and MBC[a]

Organism	Inoculum size (CFU/ml)	MIC/MBC (μg/ml)			
		ME1206	T-2525	Cefixime	Cefaclor
Staphylococcus aureus FDA 209P JC-1	6.0×10^5	0.78/1.56	6.25/6.25	50/50	3.13/12.5
Staphylococcus aureus MS15009(pI258[b])	1.2×10^6	0.39/0.39	1.56/3.13	6.25/12.5	1.56/25
Escherichia coli NIHJ JC-2	6.5×10^5	0.39/0.78	0.78/6.25	0.39/3.13	12.5/12.5
Klebsiella pneumoniae PCI-602	6.9×10^5	0.025/0.025	0.025/0.025	0.05/0.10	0.78/1.56
Klebsiella pneumoniae GN69[b]	5.6×10^5	0.39/0.78	0.39/0.39	0.10/0.10	50/100
Serratia marcescens IAM1184	8.6×10^5	0.78/3.13	1.56/6.25	0.20/0.20	>100/>100

[a] Determined by the twofold serial dilution method with sensitivity test broth.
[b] β-lactamase-producing strain.

TABLE 3. Stability of ME1206 to various β-lactamases

Enzyme source	Type of β-lactamase[a]	Relative rate of hydrolysis[b] of:					
		ME1206	T-2525	CFIX	CCL	CER	PCG
Serratia marcescens GN10857	CSase (Ia)	9.1	9.7	5.7	190	100	NT[c]
Enterobacter cloacae GN7471	CSase (Ia)	<1.0	<1.0	<1.0	110	100	NT
Morganella morganii GN5407	CSase (Ia)	2.0	2.2	<1.0	230	100	NT
Providencia rettgeri GN4430	CSase (Ia)	20	13	2.9	76	100	NT
Proteus vulgaris GN7919	CXase (Ic)	4.3	25	1.3	230	100	NT
Pseudomonas cepacia GN11164	CXase (Ic)	64	63	1.6	270	100	NT
Klebsiella oxytoca GN10650	CXase (IV)	1.6	8.3	<1.0	72	100	NT
Escherichia coli W3630(Rms212)	PCase type I (IIIa)	<1.0	<1.0	<1.0	5.7	NT	100
Escherichia coli W3630(Rms213)	PCase type II (Va)	47	85	1.7	34	NT	100
Escherichia coli ML1410(Rte16)	PCase type III (Vb)	<1.0	<1.0	<1.0	24	NT	100
Escherichia coli JM83(Rms433)	PCase type IV (Vc)	<1.0	<1.0	<1.0	<1.0	NT	100
Staphylococcus aureus MS15009(pI258)	PCase type V	<1.0	<1.0	<1.0	9.6	NT	100

[a] See reference (10). Abbreviations: CSase, cephalosporinase; CXase, oxyiminocephalosporinase; PCase, penicillinase. Richmond and Sykes classification (14) is shown in parentheses.

[b] Relative site of hydrolysis is expressed as the percentage of hydrolysis of cephaloridine or benzylpenicillin. Abbreviations: CFIX, cefixime; CCL, cefaclor, CER, cephaloridine; PCG, benzylpenicillin.

[c] NT, Not tested.

activity of the compounds was determined by measuring their protective effect against systemic infections in mice. Ten male ICR mice weighing 19 to 21 g were used for each dose. An overnight culture on heart infusion agar plate (Nissui Seiyaku) at 37°C was suspended in 0.85% NaCl or in 2.5% gastric mucin. A 0.5-ml volume of bacterial suspension, equal to 10 to 80 times higher than the 50% lethal dose, was inoculated intraperitoneally. Under these conditions, untreated mice died within 48 h. The compounds were suspended in 0.5% carboxymethyl cellulose and given as a single oral dose to the mice immediately after infection. Survivors were recorded on day 5 after infection. The 50% effective doses were calculated by the probit method (8).

Serum concentrations and urinary excretion in mice. Three 4-week-old male ICR mice weighing 19 to 21 g were used for each antibiotic. Each antibiotic was suspended in 0.5% carboxymethylcellulose and given as a single oral dose (25 mg/kg of body weight) to each mouse. Serum concentrations were obtained from mice at 15 min, 30 min, and 1, 2, 4, and 6 h after antibiotic administration. Excreted urines were obtained from three mice in a group that were placed in a metabolism cage (Sugiyamagen Co., Tokyo, Japan) at 2, 4, 6, and 24 h after antibiotic administration. Serum and urinary drug concentrations were determined by a bioassay method. The test organism for ME1206, T-2525, and cefixime was *Escherichia coli* K-12 8236, and for cefaclor it was *Micrococcus luteus* PCI 1001.

RESULTS

Antibacterial activity. The MICs of ME1206 against clinical isolates were compared with those of T-2525, cefixime, and cefaclor (Table 1). The MICs of ME1206 at which 90% of isolates were inhibited (MIC_{90}s) were 0.78 and 6.25 μg/ml for methicillin-susceptible *Staphylococcus aureus* and *Staphylococcus epidermidis*, respectively. At this level, ME1206 was 2 to 4 times more active than cefaclor, 4 times more active than T-2525, and 16 times more active than cefixime. But ME1206 showed poor activity against methicillin-resistant *Staphylococcus aureus* (MIC_{90}, 100 μg/ml). Against *Streptococcus pneumoniae* and *Streptococcus pyogenes*, ME1206 exhibited excellent activity (MIC_{90}, ≦0.025 μg/ml). ME1206 had poor activity against *Enterococcus faecalis* (MIC_{90}, 100 μg/ml).

ME1206 was highly active against various species of gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Salmonella* spp., *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*. Its activity was comparable to that of T-2525 and inferior to that of cefixime. Against *Citrobacter freundii* and *Enterobacter cloacae*, several strains were less susceptible to ME1206, but ME1206 inhibited these organisms at a concentration lower than that of any other compound tested. Against *Serratia marcescens*, ME1206 had good activity (MIC_{90}, 6.25 μg/ml), but cefixime was more active than ME1206. Against *Pseudomonas aeruginosa*, *Pseudomonas maltophilia*, and *Acinetobacter* spp. (MIC_{90}s, 100, >100, and 100 μg/ml, respectively), ME1206 had poor activity. Against *Pseudomonas cepacia*, ME1206 had good activity (MIC_{90}, 6.25 μg/ml). Against *Haemophilus influenzae* and *Neisseria gonorrhoeae*, ME1206 had strong activity (MIC_{90}s, ≦0.025 and 0.05 μg/ml, respectively). Against *Bacteroides fragilis*, ME1206 showed broad activities (MIC range, 0.78 to 100 μg/ml).

Bactericidal activity. The bactericidal activity of ME1206 is shown in Table 2. The MBC values of ME1206 against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Serratia marcescens* were identical to or two to four times as high as the MIC values.

Stability against β-lactamases. Hydrolysis of ME1206 by various types of β-lactamases was expressed as the relative

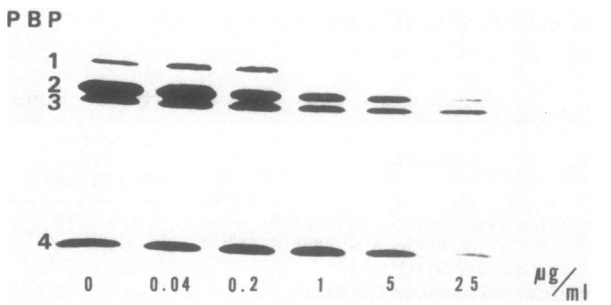

FIG. 2. Results of fluorography by competition of ME1206 at concentrations of 0.04, 0.2, 1, 5, and 25 μg/ml (shown below lanes) with ^{14}C-labeled penicillin G for binding to the PBPs of *Staphylococcus aureus* FDA 209P JC-1.

TABLE 4. Protective effect of ME1207 on systemic infections in mice

Organism	Inoculum size[a] (CFU/mouse)	Compound[b]	ED_{50}[c] (95% confidence limit) (mg/kg of body weight)	MIC (μg/ml)
Staphylococcus aureus Smith	1.2×10^6 ($24 \times LD_{50}$)	ME1207	10 (7.5–14)	0.39[d]
		T-2588	44 (28–58)	3.13[e]
		Cefixime	55 (45–91)	12.5
		Cefaclor	0.25 (0.20–0.34)	0.78
Escherichia coli ML4707	1.2×10^7 ($67 \times LD_{50}$)	ME1207	2.5 (1.8–3.6)	0.10[d]
		T-2588	3.1 (2.2–4.5)	0.10[e]
		Cefixime	1.4 (0.87–1.7)	0.20
		Cefaclor	10 (7.3–14)	1.56
Klebsiella pneumoniae GN6445	2.7×10^7 ($10 \times LD_{50}$)	ME1207	11 (7.4–16)	0.20[d]
		T-2588	11 (8.0–15)	0.20[e]
		Cefixime	0.75 (0.55–1.0)	0.05
		Cefaclor	18 (11–27)	0.78
Proteus mirabilis GN4754	2.9×10^7 ($40 \times LD_{50}$)	ME1207	4.4 (2.9–6.7)	0.10[d]
		T-2588	4.8 (3.3–7.5)	0.05[e]
		Cefixime	0.50 (0.40–0.67)	<0.006
		Cefaclor	6.5 (4.8–8.5)	0.39
Serratia marcescens GN14931	1.2×10^7 ($80 \times LD_{50}$)	ME1207	11 (7.7–15)	0.78[d]
		T-2588	18 (12–17)	0.78[e]
		Cefixime	0.95 (0.51–1.5)	0.39
		Cefaclor	>100	>100

[a] Administered intraperitoneally with 2.5% gastric mucin, except *E. coli* and *K. pneumoniae*, which were administered without gastric mucin. LD_{50}, 50% lethal dose.
[b] Single oral dose immediately after infection.
[c] ED_{50}, 50% effective dose.
[d] MIC of ME1206.
[e] MIC of T-2525.

rate of hydrolysis, with 100 being the absolute rate of hydrolysis of cephaloridine or benzylpenicillin (Table 3). ME1206 was stable against β-lactamases from *Enterobacter cloacae* and *Morganella morganii*, but ME1206 was slightly hydrolyzed by β-lactamases from *Serratia marcescens* and *Providencia rettgeri*. ME1206 was unstable against β-lactamase from *Pseudomonas cepacia*. ME1206 was highly stable against several types of R plasmid-mediated β-lactamase, but ME1206 was unstable against plasmid Rms213-mediated β-lactamase. ME1206 was highly stable against β-lactamase produced by *Staphylococcus aureus*. In general, the stabilities of ME1206 against various β-lactamases were much greater than those of cefaclor and were comparable with or better than those of T-2525 against all the enzymes except the *Providencia rettgeri* β-lactamase.

Binding affinity for PBPs. The binding affinity of ME1206 for PBPs of *Staphylococcus aureus* FDA 209P JC-1 was determined. The results of fluorography by competition of ME1206 with ^{14}C-labeled penicillin G for PBPs are shown in Fig. 2. ME1206 possessed high affinities for PBP 2 (I_{50}, 0.13 μg/ml), PBP 1 (I_{50}, 0.50 μg/ml), and PBP 3 (I_{50}, 1.7 μg/ml) but low affinity for PBP 4 (I_{50}, 12 μg/ml).

In vivo efficacy. The protective effects of ME1207 on systemic infections in mice are shown in Table 4. The 50% effective dose of ME1207 against *Staphylococcus aureus* Smith infection was 10 mg/kg; ME1207 was four to six times as active as T-2525 and cefixime, but cefaclor was the most effective (0.25 mg/kg). The 50% effective doses of ME1207 against *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Serratia marcescens* were comparable with those of T-2525 and were inferior to those of cefixime.

Concentrations in serum and urinary excretion in mice. Concentrations of antibiotics in serum and urinary excretion of antibiotics by mice are shown in Fig. 3 and 4, respectively. The concentration of ME1206 in serum was 16.6 μg/ml at the peak level. Urinary excretion of ME1206 by mice amounted to 18% of the initial dose during the 24 h after administration.

DISCUSSION

Recently, several new oral cephalosporins, such as cefixime, T-2588, and CS-807, have been developed. Cefixime

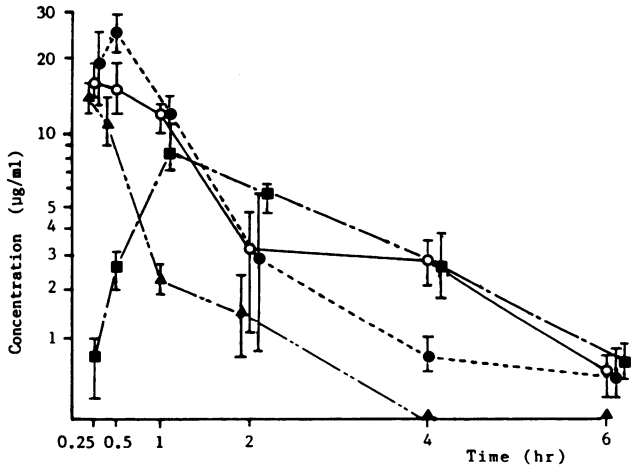

FIG. 3. Levels of ME1206 (○), T-2525 (●), cefixime (■), and cefaclor (▲) in serum after oral administration to mice of 25 mg of each antibiotic per kg of body weight. Data shown represent means ± standard errors.

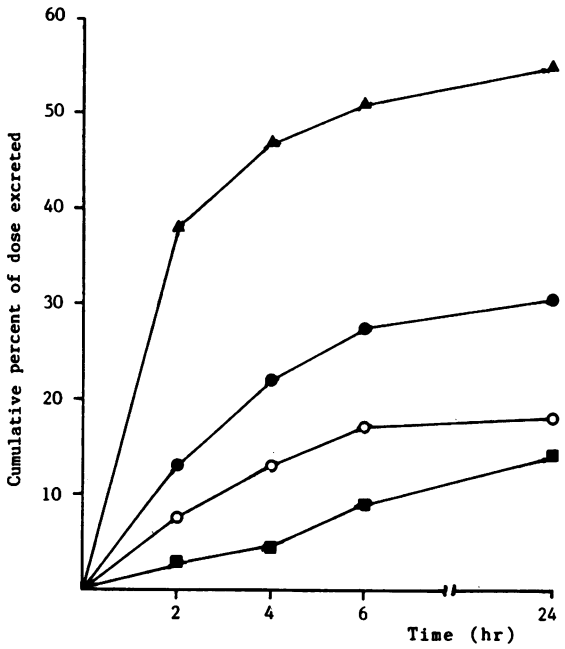

FIG. 4. Level of urinary excretion of ME1206 (○), T-2525 (●), cefixime (■), and cefaclor (▲) after oral administration to mice of 25 mg of each antibiotic per kg of body weight.

has an α-acetoxyimino aminothiazole side chain at the 7-position of the cephem nucleus. T-2525 and R-3746 (active forms of T-2588 and CS-807, respectively) have α-methoxyimino aminothiazole side chains. ME1206 has the same side chain. These antibiotics have highly potent antibacterial activity against various species of gram-negative bacteria.

ME1206 has excellent antibacterial activity against gram-positive bacteria in addition to gram-negative bacteria. Its antibacterial activity, especially against staphylococci, is superior to those of T-2525 and cefaclor. ME1206 had high affinity to PBPs 1, 2, and 3 of *Staphylococcus aureus*. ME1206 is stable against β-lactamase produced by *Staphylococcus aureus*, but cefaclor is unstable against the same enzyme.

ME1207 had therapeutic effects comparable with those of T-2588 against systemic infections in mice with various species of bacteria. When ME1207 was administered orally, the concentration in serum of ME1206 was almost comparable with those of T-2525, cefixime, and cefaclor in mice. However, cefaclor had better activity than ME1207 against systemic infection of *Staphylococcus aureus* Smith, and cefixime had better activity than ME1207 against systemic infections of gram-negative bacteria. It is impossible to explain these points on the basis of serum concentrations of these antibiotics. Other factors might be involved in therapeutic effects in mice.

Considering these results, further studies and clinical trials of ME1207 are warranted.

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