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In Vitro Activity and β-Lactamase Stability of Two Oral Cephalosporins, Ceftetrame (Ro 19-5247) and Cefetamet (Ro 15-8074)

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Ceftetrame (Ro 19-5247) and cefetamet (Ro 15-8074), two new orally administered aminothiazolyl imimomethoxy cephalosporins, inhibited hemolytic streptococci and *Streptococcus pneumoniae* at ≤0.5 μg/ml but were less active against staphylococci than were cephalexin and cefaclor. They did not inhibit *S. faecalis*, *S. faecium*, *Listeria monocytogenes*, *Corynebacterium* JK species, or *Pseudomonas aeruginosa*. *Haemophilus influenzae*, *Branhamella catarrhalis*, and *Neisseria gonorrhoeae*, including ampicillin-resistant isolates, were inhibited at <0.25 μg/ml. Both agents inhibited *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Proteus mirabilis*, *Salmonella* species, *Shigella* species, *Citrobacter diversus*, and *Aeromonas hydrophila* resistant to ampicillin, cephalexin, and cefaclor at ≤2 μg/ml, although many isolates of *Enterobacter cloacae*, *Citrobacter freundii*, and *Serratia marcescens* resistant to cefotaxime were not inhibited by these agents. A marked inoculum effect was noted for *Enterobacteriaceae* carrying the Richmond-Sykes type 1A chromosomally mediated beta-lactamases, but plasmid-mediated beta-lactamases did not hydrolyze the compounds. Both drugs inhibited the chromosomally mediated beta-lactamase of *E. cloacae*, P99.

Although there has been great progress in the development of parenteral cephalosporins stable to attack by beta-lactamases and active against a wide spectrum of gram-positive and -negative bacteria, this goal has not been achieved for oral cephalosporins (2). The early oral cephalosporins, cephalexin and cephradine, although moderately stable to attack by beta-lactamases, have had relatively poor activity against important respiratory pathogens such as *Haemophilus influenzae* and *Branhamella catarrhalis* (1, 7). Furthermore, their activity against *Streptococcus pneumoniae* is significantly lower than that of the parenteral cephalosporins, and these compounds do not inhibit many beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* important as causes of nosocomial urinary tract infections. Cefaclor, which has activity against *H. influenzae*, unfortunately is not beta-lactamase stable. Ceftetrame (Ro 19-5247) and cefetamet (Ro 15-8074) are new aminothiazolyl iminomethoxy cephalosporins similar to cefotaxime in terms of the β-acyl side chain. The compounds are the biologically active products of orally administered prodrugs. We wished to compare the activities of these new cephalosporins with those of other oral antibiotics and with that of cefotaxime as a parenteral agent against a variety of bacteria for which an oral cephalosporin could be used as initial or follow-up therapy to a broad-spectrum parenteral agent.

MATERIALS AND METHODS

Microorganisms. The gram-positive and -negative bacteria used in this study were clinical isolates collected at The Columbia-Presbyterian Medical Center, New York, N.Y.

Antimicrobial agents. Standard antimicrobial powders were provided as follows: ceftetrame, cefetamet, and trimethoprim from Hoffmann-La Roche Inc., Nutley, N.J.; cephalexin and cefaclor from Eli Lilly & Co., Indianapolis, Ind.; cefotaxime from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; amoxicillin and amoxicillin-clavulanate from Beecham Laboratories, Bristol, Tenn.; and gentamicin from Schering Corp., Kenilworth, N.J. Antimicrobial solutions were prepared on the day of use as directed by the manufacturers.

Susceptibility studies. Susceptibility testing was performed by a standard agar dilution technique using Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with 5% defibrinated sheep blood for testing streptococci and with 5% chocolate blood for testing *Haemophilus*, *Branhamella*, or *Neisseria* species. Brucella agar supplemented with hemin and vitamin K was used for anaerobic species. Overnight cultures of test organisms in Mueller-Hinton broth (BBL), Todd-Hewitt broth (BBL) for streptococci, Schaedler broth for *Haemophilus* and *Neisseria* spp., or chopped meat-glucose (Scott Laboratories, Inc., Providence, R.I.) for anaerobic species were diluted in Mueller-Hinton broth. Final inocula of approximately 10^5 CFU were applied to plates by a multipoint spot inoculator. Plates were examined after 18 h of incubation of 35°C. Anaerobic organisms were incubated in GasPak jars (BBL) for 48 h at 35°C. Susceptibilities to all agents were tested at the same time.

Susceptibilities of five isolates each of several bacterial species to ceftetrame and cefetamet were determined by the broth dilution technique. Tubes (1 ml) containing serial twofold dilutions of the compounds in Mueller-Hinton broth were inoculated with log-phase organisms to yield a final inoculum of approximately 5×10^5 CFU/ml. Tubes were incubated for 18 h at 35°C and inspected for lack of turbidity. Samples of 0.01 ml were removed to antibiotic-free plates which were incubated for 24 h at 35°C. The MBC, defined as 99.9% reduction of the initial inoculum, was determined by the method of Pearson et al. (6) assuming a 5% pipetting error. Organisms were considered resistant to ampicillin, cephalexin, and cefaclor if MICs were ≥16 μg/ml.

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TABLE 1. Comparative activities of ceftetrame, cefetamet, and other antimicrobial agents against gram-positive bacteria

Organism (no. of isolates)	Drug	MIC (μg/ml)		
		Range	50%	90%
Staphylococcus aureus, methicillin susceptible (20)	Ceftetrame	2–>32	4	16
	Cefetamet	16–>32	>32	>32
	Cephalexin	0.12–>32	2	8
	Cefaclor	0.5–16	2	8
	Cefotaxime	1–4	2	4
Staphylococcus epidermidis, methicillin susceptible (20)	Ceftetrame	0.5–>32	4	>32
	Cefetamet	0.5–>32	8	>32
	Cephalexin	0.25–>32	1	8
	Cefaclor	0.25–4	≤0.5	2
	Cefotaxime	0.25–16	2	8
Streptococcus pyogenes (25)	Ceftetrame	≤0.015–0.25	≤0.015	0.25
	Cefetamet	≤0.015–1	0.03	0.5
	Cephalexin	0.06–4	0.25	4
	Cefaclor	0.06–4	≤0.06	2
	Cefotaxime	≤0.015–0.125	≤0.015	0.06
Streptococcus agalactiae (20)	Ceftetrame	≤0.015–2	0.125	0.25
	Cefetamet	0.5–2	1	1
	Cephalexin	1–8	2	4
	Cefaclor	0.125–2	0.5	1
	Cefotaxime	≤0.015–0.06	≤0.015	0.03
Streptococcus groups C, F, and G (45)	Ceftetrame	≤0.015–4	0.25	2
	Cefetamet	≤0.015–4	0.125	2
	Cephalexin	0.125–8	1	8
	Cefaclor	0.125–8	0.5	8
	Cefotaxime	≤0.015–0.125	≤0.015	0.125
Streptococcus bovis (20)	Ceftetrame	0.25–2	0.5	2
	Cefetamet	0.5–4	4	4
	Cephalexin	0.5–32	1	32
	Cefaclor	0.125–32	0.25	32
	Cefotaxime	0.125–0.5	0.125	0.25
Streptococcus pneumoniae (20)	Ceftetrame	0.06–0.25	0.06	0.06
	Cefetamet	0.06–0.25	0.25	0.25
	Cephalexin	0.5–2	1	2
	Cefaclor	0.25–1	0.25	1
	Cefotaxime	0.015–0.25	0.015	0.25
Listeria monocytogenes (20)	Ceftetrame	8–>32	8	>32
	Cefetamet	2–>32	16	32
	Cephalexin	>32	>32	>32
	Cefaclor	>32	>32	>32
	Cefotaxime	8–>32	>32	>32

Beta-lactamase assays and inhibition studies. The presence of beta-lactamases in clinical isolates was determined by the nitrocefin assay (3). Beta-lactamases used for determination of the stability of the compounds were either purified enzymes or partially purified enzymes as previously described (3). The stabilities of the compounds to beta-lactamase were determined by spectrophotometric assay by using the change in absorption at the absorption maximum of each substrate. The absorption used for ceftetrame and for cefetamet was 265 nm. Inhibition assays with nitrocefin as the substrate, 10^{-4} M concentration, were performed in a final volume of 3 ml. Enzyme and inhibitor were incubated at various concentrations at 35°C for 10 min, and subsequently nitrocefin was added. Change in the A_{482} of nitrocefin was monitored for 10 min in a temperature-controlled recording spectrophotometer. As a control, the change in nitrocefin plus enzyme was monitored.

RESULTS

The activities of ceftetrame and cefetamet against gram-positive organisms are shown in Table 1. Although ceftetrame inhibited 50% of *S. aureus* at 4 μg/ml, it and cefetamet both required higher concentrations to inhibit *S. aureus* than did the other oral cephalosporins or cefotaxime, with MICs for 90% of the organisms tested of 16 and >32 μg/ml, respectively. Neither agent inhibited methicillin-resistant *S. aureus* (data not shown), and most *S. epidermidis* strains were resistant. In contrast, both agents showed excellent activity against hemolytic streptococcal species. Ceftetrame usually was twofold more active than cefetamet, and both were more active or as active as cefaclor and cephalexin. Neither agent was as active as cefotaxime or amoxicillin (data not shown). *Streptococcus faecalis*, *S. faecium*, and *Corynebacterium* JK organisms were resistant

TABLE 2. Comparative activities of ceftetrame, cefetamet, and other antimicrobial agents against aerobic gram-negative bacteria and anaerobic species

Organism (no. tested)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Escherichia coli (25)	Ceftetrame	0.125–1	0.25	1
	Cefetamet	0.125–8	0.5	2
	Cephalexin	8–128	8	64
	Cefaclor	4–128	8	64
	Cefotaxime	0.125–1	0.125	0.125
Klebsiella pneumoniae (25)	Ceftetrame	0.125–4	0.25	1
	Cefetamet	0.06–1	0.125	0.25
	Cephalexin	4–128	4	16
	Cefaclor	4–128	4	16
	Cefotaxime	0.03–4	0.03	0.125
Klebsiella oxytoca (20)	Ceftetrame	0.125–0.25	0.125	0.25
	Cefetamet	0.06–0.5	0.125	0.25
	Cephalexin	4–128	4	128
	Cefaclor	0.125–128	0.5	128
	Cefotaxime	0.015–0.06	0.03	0.06
Enterobacter aerogenes and *Enterobacter cloacae* (45)	Ceftetrame	0.125–>128	0.5	>128
	Cefetamet	0.25–>128	1	32
	Cephalexin	>128	>128	>128
	Cefaclor	>128	>128	>128
	Cefotaxime	0.03–64	0.25	32
Enterobacter agglomerans (15)	Ceftetrame	1–4	1	4
	Cefetamet	0.125–4	1	4
	Cephalexin	8–>128	>128	>128
	Cefaclor	8–>128	>128	>128
	Cefotaxime	0.06–4	0.25	2
Hafnia alveii (10)	Ceftetrame	2–8	2	8
	Cefetamet	8–16	8	16
	Cephalexin	>128	>128	>128
	Cefaclor	>128	>128	>128
	Cefotaxime	0.5–1	0.5	1
Salmonella spp. (20)	Ceftetrame	0.125–4	0.25	1
	Cefetamet	0.5–16	0.5	2
	Cephalexin	8–32	8	32
	Cefaclor	2–32	4	32
	Cefotaxime	0.015–1	0.06	0.125
Shigella spp. (15)	Ceftetrame	0.06–1	0.125	0.5
	Cefetamet	0.25–2	0.5	1
	Cephalexin	4–16	8	16
	Cefaclor	2–32	4	16
	Cefotaxime	0.12–1	0.12	0.25
Serratia marcescens (25)	Ceftetrame	0.5–>16	2	16
	Cefetamet	0.5–>128	2	16
	Cephalexin	>128	>128	>128
	Cefaclor	>128	>128	>128
	Cefotaxime	0.125–64	0.5	16
Citrobacter freundii (25)	Ceftetrame	0.25–64	0.5	64
	Cefetamet	1–>128	2	64
	Cephalexin	>128	>128	>128
	Cefaclor	32–>128	64	>128
	Cefotaxime	0.125–64	0.125	1
Citrobacter diversus (15)	Ceftetrame	0.125–1	0.25	1
	Cefetamet	0.125–2	0.5	1
	Cephalexin	4–>128	0.25	1
	Cefaclor	0.5–16	1	16
	Cefotaxime	0.015–0.125	0.03	0.06

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TABLE 2—*Continued*

Organism (no. tested)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Proteus mirabilis (25)	Ceftetrame	0.03–0.5	0.06	0.25
	Cefetamet	0.125–8	1	2
	Cephalexin	1–>128	4	16
	Cefaclor	1–>128	2	16
	Cefotaxime	0.015–0.06	0.015	0.06
Proteus vulgaris (20)	Ceftetrame	0.06–>16	0.125	4
	Cefetamet	0.03–>128	0.125	8
	Cephalexin	16–>128	128	>128
	Cefaclor	16–>128	128	>128
	Cefotaxime	0.06–8	0.125	8
Morganella morganii (25)	Ceftetrame	0.06–>128	8	64
	Cefetamet	0.03–>128	0.125	8
	Cephalexin	8–>128	>128	>128
	Cefaclor	8–>128	>128	>128
	Cefotaxime	0.125–32	0.125	1
Providencia rettgeri (20)	Ceftetrame	0.06–16	1	8
	Cefetamet	0.06–32	0.125	8
	Cephalexin	128–>128	>128	>128
	Cefaclor	128–>128	>128	>128
	Cefotaxime	0.06–1	0.06	1
Providencia stuartii (25)	Ceftetrame	0.03–16	0.25	4
	Cefetamet	0.03–16	0.06	0.5
	Cephalexin	32–>128	128	>128
	Cefaclor	32–>128	128	>128
	Cefotaxime	0.03–2	0.125	0.5
Acinetobacter spp. (25)	Ceftetrame	4–>128	8	>128
	Cefetamet	4–>128	8	>128
	Cephalexin	>128	>128	>128
	Cefaclor	>128	>128	>128
	Cefotaxime	4–>128	8	>128
Aeromonas hydrophila (10)	Ceftetrame	0.03–8	0.125	15
	Cefetamet	0.03–8	0.25	0.5
	Cephalexin	>128	>128	>128
	Cefaclor	>128	>128	>128
	Cefotaxime	≤0.06	≤0.06	≤0.06
Yersinia enterocolitica (10)	Ceftetrame	0.125–16	0.125	1
	Cefetamet	0.06–16	0.125	1
	Cephalexin	4–>128	16	>128
	Cefaclor	0.5–>128	32	>128
	Cefotaxime	0.06–2	0.06	0.06
Branhamella catarrhalis (15)	Ceftetrame	0.125–2	0.25	0.5
	Cefetamet	0.25–2	0.25	0.5
	Cephalexin	4–8	4	8
	Cefaclor	0.03–4	0.5	2
	Cefotaxime	0.03–0.12	0.03	0.12
Haemophilus influenzae type b (20)	Ceftetrame	0.03–0.12	0.03	0.12
	Cefetamet	0.06–0.25	0.125	0.25
	Cephalexin	1–32	8	16
	Cefaclor	0.5–16	2	8
	Cefotaxime	0.015–0.06	0.03	0.06
Neisseria gonorrhoeae (15)	Ceftetrame	≤0.03–0.25	≤0.03	0.12
	Cefetamet	≤0.03–0.25	0.12	0.25
	Cefotaxime	≤0.03	≤0.03	≤0.03
Neisseria meningitidis (10)	Ceftetrame	≤0.03–0.12	≤0.03	0.12
	Cefetamet	≤0.03	≤0.03	≤0.03
	Cefotaxime	≤0.03	≤0.03	≤0.03

TABLE 3. Effect of inoculum size on the MICs and MBCs of cefetamet

Organism[a]	Geometric mean of MIC/MBC (μg/ml) at an inoculum size (CFU/ml) of:	
	10^5	10^7
E. coli	0.5/0.84	0.79/2.83
K. pneumoniae	0.84/2	1.19/19.03
E. cloacae	32/64	>64/>128
C. freundii	2/2.8	22.63/90.51
S. marcescens	4/9.51	38.05/>38.05
M. morganii	5.66/11.31	>128/>128
P. vulgaris	64/64	>128/>128

[a] Five organisms of each species, all beta-lactamase positive.

to both agents (data not shown), as was *Listeria monocytogenes*.

Ceftetrame and cefetamet inhibited organisms such as *E. coli*, *K. pneumoniae*, *K. oxytoca*, *Salmonella* sp., *Shigella* sp., *Citrobacter diversus*, *Proteus mirabilis*, *Aeromonas hydrophila*, and *Yersinia enterocolitica* at concentrations ≤2 μg/ml (Table 2). Both agents were more active than cephalexin, cefaclor, and ampicillin (data not shown) against these species, many of which contained beta-lactamases as determined by nitrocefin testing. In general, cefotaxime was severalfold more active than either ceftetrame or cefetamet. Although both of these new agents inhibited 50% of *Enterobacter* species, *C. freundii*, and *Serratia marcescens* at ≤4 μg/ml, the MICs of 25% of these three species exceeded 16 μg/ml. All of the aforementioned organisms were resistant to cefaclor and cephalexin, and some isolates were also resistant to cefotaxime. MICs of 25% of *P. vulgaris*, *Morganella morganii*, and *Providencia rettgeri* were 4 to 8 μg/ml, considerably higher than the concentrations required to inhibit *P. mirabilis*.

Neither ceftetrame nor cefetamet inhibited *Pseudomonas aeruginosa*, *P. maltophilia*, and *P. cepacia* (data not shown), and 50% of *Acinetobacter* sp. had MICs >8 μg/ml. *Achromobacter xylosoxidans* and *Flavobacterium* sp. (two isolates each) (data not shown) were resistant, but *K. ozaenae* and *Enterobacter sakazakii* (two isolates each) were inhibited by ≤0.25 μg/ml.

Both ceftetrame and cefetamet had excellent activity against *H. influenzae* and *Neisseria gonorrhoeae*, including beta-lactamase-positive isolates, and both agents were more active than cephalexin or cefaclor against *B. catarrhalis*. Both agents had poor activity against *Bacteroides* species, with MICs for 50 and 90% of the organisms tested of 16 and 32 μg/ml, respectively. The majority of *Clostridium* species had MICs ≥32 μg/ml.

Overall, ceftetrame and cefetament inhibited 76% of amoxicillin-resistant *Enterobacteriaceae* and 66% of cephalexin-resistant strains at ≤2 μg/ml. The cephalexin-cefaclor-resistant isolates which were resistant to these two agents were *E. cloacae*, *C. freundii*, *S. marcescens*, *M. morganii*, and *Providencia* spp. The agents also inhibited some *E. coli* and *K. pneumoniae* resistant to trimethoprim and some of the *Enterobacteriaceae* resistant to gentamicin (data not shown).

Effect of assay conditions on activity. The type of agar medium used to determine the MICs (Mueller-Hinton, brain heart infusion, tryptic digest) did not yield more than a twofold difference in the activity of either agent against five strains each of *S. aureus*, *E. coli*, *K. pneumoniae*, *M. morganii*, *E. cloacae*, and *S. marcescens*. Similarly, MICs were not appreciably changed when the pH of Mueller-Hinton agar medium was adjusted to pH 6, 7, or 8.

The effect of inoculum size was determined with inocula of 10^5 and 10^7 CFU. For cefetamet, the MIC increased at 10^7 CFU to resistant levels with organisms such as *E. cloacae*, *C. freundii*, *S. marcescens*, *M. morganii*, and *P. vulgaris* (Table 3). Similarly, for ceftetrame (data not shown) the MICs at 10^7 CFU increased eightfold or more for 41% of the 35 isolates tested, and the MBC/MIC ratio was >2. However, the MBCs of both ceftetrame and cefetamet were within twofold of the MICs for 93% of the 35 isolates when tested at an inoculum of 10^5 CFU.

Beta-lactamase stability and inhibition. The beta-lactamase stabilities of ceftetrame and cefetamet are compared with those of other cephalosporins in Table 4. Both agents were more stable than cefaclor or cephalexin and compared favorably with cefotaxime. They were not hydrolyzed by TEM or SHV-1 plasmid beta-lactamases and were stable to attack by the Richmond-Sykes type Ia beta-lactamases under the conditions of the assay. Like cefotaxime, the compounds were hydrolyzed by *P. vulgaris* beta-lactamase.

Both compounds had great affinity for the *E. cloacae* and *P. aeruginosa* beta-lactamases, as shown by their inhibition of these enzymes (Table 5). But neither compound was an effective inhibitor of the TEM-1, SHV-1, K-1, or type V beta-lactamases at a concentration that effectively inhibited the *E. cloacae* beta-lactamase.

TABLE 4. Beta-lactamase stabilities of ceftetrame and cefetamet compared with those of other cephalosporins

Beta-lactamase	Source organism	Type[a]	Richmond-Sykes classification	Relative rate of hydrolysis[b]				
				Ceftetrame	Cefetamet	Cefotaxime	Cefaclor	Cephalexin
TEM-1	*E. coli*	P	IIIa	0.5	≤0.1	≤0.1	20	1
SHV-1	*K. pneumoniae*	P	IIIa	≤0.1	≤0.1	≤0.1	12	<0.01
P99	*E. cloacae*	C	Ia	≤0.1	≤0.1	≤0.1	40	30
	M. morganii	C	Ia	≤0.1	2.4	<0.1		
	P. vulgaris	C	Ic	98	47	47		
	C. freundii	C	Ia	≤0.1	≤0.1	1		
K1	*K. oxytoca*	C	IV	8	4.6	<0.1	55	30
PSE-4	*P. aeruginosa*	P	V	<0.1	0.1	<0.1	25	1
OXA-2	*P. aeruginosa*	P	V	<0.1	0.1	<0.1	100	10
Sabath-	*P. aeruginosa*	C	Id	≤0.1	≤0.1	≤0.1	37	22
Abraham	*B. catarrhalis*	P		≤0.1	≤0.1	<0.1	68	47
PC1	*S. aureus*	P		≤0.1	≤0.1	≤0.1	38	27

[a] C, Chromosomal; P, plasmid.
[b] Cephaloridine = 100.

TABLE 5. Inhibition hydrolysis of beta-lactamases by ceftetrame and cefetamet

Beta-lactamase	Source organism	Richmond-Sykes classification	% Inhibition of nitrocefin hydrolysis[a]	
			Ceftetrame	Cefetamet
TEM-1	*E. coli*	IIIa	0	10.4
SHV-1	*K. pneumoniae*	IIIa	0	0
P99	*E. cloacae*	Ia	94	95
Sabath-Abraham	*P. aeruginosa*	Id	97	86
Kl	*K. oxytoca*	IV	0	0
PSE-4	*P. aeruginosa*	V	0	0
OXA-2	*P. aeruginosa*	V	0	2.6

[a] The concentration of nitrocefin, ceftetrame, and cefetamet was 100μM. The compounds were preincubated with enzyme for 10 min at 35°C before nitrocefin was added.

DISCUSSION

Cephalosporins which possess an aminothiazolyl moiety on the β-acyl side chain have excellent in vitro activity against *H. influenzae*, *N. gonorrhoeae*, *Enterobacteriaceae*, and streptococci with the exception of enterococci (2). The presence of an iminomethoxy group has provided the agents with beta-lactamase stability against most plasmid-mediated beta-lactamases and many chromosomal beta-lactamases (2, 4). Ceftetrame and cefetamet are the products yielded when orally absorbed esters are ingested. Both agents showed excellent activity against important streptococci with poor activity against staphylococci. They were more active than currently available oral cephalosporins such as cephalexin and cefaclor against streptococci and *S. pneumoniae*. The major advance of ceftetrame and cefetamet is against the *Enterobacteriaceae*, particularly isolates resistant to ampicillin and cephalexin. Although the majority of the *Enterobacteriaceae* were inhibited by ≤2 μg/ml, these agents were less active than cefotaxime against some *Enterobacter*, *Citrobacter*, and *Serratia* isolates, and these new agents did not inhibit any isolates of these species that are resistant to cefotaxime, nor did they inhibit *Pseudomonas*, many *Acinetobacter*, or *Bacteroides* species. The compounds were much more active than cefaclor or cephalexin against *H. influenzae* and *N. gonorrhoeae* and inhibited beta-lactamase-producing isolates of these species. Our results are similar to those of Ng et al. (5) against *N. gonorrhoeae*.

Like the other iminomethoxy cephalosporins, these agents were not hydrolyzed by the most common plasmid beta-lactamase, TEM-1. They were not destroyed by chromosomal beta-lactamases under the conditions of the assay, but they have a high affinity for these enzymes, and there undoubtedly is destruction as with other agents (9, 10). This would explain the inoculum effects seen with organisms such as *Enterobacter* and *Citrobacter* species.

Why these agents were less active against some *Morganella* isolates is not known since they were not readily destroyed by a purified *M. morganella* beta-lactamase. This had been previously noted for cefixime, another orally administered beta-lactamase-stable cephalosporin (4).

Overall, both compounds had in vitro activity similar to that which we had noted for the oral cephalosporin cefixime (FR 17027) (4). The differences between ceftetrame and cefetamet are relatively minor, although ceftetrame may be overall slightly more active against a greater number of isolates.

These agents may prove useful for treating selected upper respiratory infections in which streptococci, *H. influenzae* and *B. catarrhalis* are common and *S. aureus* is less frequent. The compounds also may have a potential for treatment of infections due to *Enterobacteriaceae* resistant to currently available beta-lactams. Further pharmacological and clinical studies should establish the merits of these orally administered aminothiazolyl cephalosporins and whether they will be a problem because of selection of species which make chromosomally mediated beta-lactamases (8).

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