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Comparative In Vitro Activity and β-Lactamase Stability of FK482, a New Oral Cephalosporin

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FK482 is an oral aminothiazolyl hydroxyimino cephalosporin with a C-3 vinyl group. Its activity was compared with those of cephalexin, cefuroxime, cefixime, and amoxicillin-clavulanate. FK482 inhibited 90% of *Staphylococcus aureus* isolates at 1 μg/ml and 90% of *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus pneumoniae* isolates at ≤0.012 μg/ml, superior to cephalexin and cefuroxime and similar to cefixime. It did not inhibit oxacillin-resistant *S. aureus*. FK482 inhibited 90% of *Enterococcus faecalis* isolates at 8 μg/ml. Although 90% of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella* species, and *Shigella* species isolates were inhibited by ≤2 μg/ml, FK482 was less active than cefixime against *Citrobacter*, *Enterobacter*, *Morganella*, *Serratia*, and *Providencia* species, with MICs for many isolates of >8 μg/ml. FK482 inhibited *Haemophilus influenzae* and *Neisseria gonorrhoeae* at concentrations comparable to that of cefixime and superior to those of cephalexin and cefaclor. *Bacteroides* and *Pseudomonas* species were resistant. FK482 was not hydrolyzed by the TEM-1 and TEM-2 β-lactamases but was hydrolyzed by TEM-3 and the *Proteus vulgaris* enzyme. It had a high affinity for chromosomal β-lactamases.

A number of oral cephalosporins have been developed in the past several years (1–4, 8, 9). The early oral cephalosporins, cephalexin, cephradine, and cefadroxil, have continued to be used worldwide, but only cefaclor and recently cefuroxime axetil have been used to treat respiratory infections due to *Haemophilus influenzae*. Cefixime has undergone extensive clinical evaluation and has been used to treat infections due to β-lactamase-producing bacteria (5), but it lacks activity against *Staphylococcus aureus* (4, 8).

We wished to evaluate the activity of FK482 (Fig. 1), an aminothiazolyl hydroxyimino cephalosporin with a C-3 vinyl group, and to compare it with those of other orally administered cephalosporins and amoxicillin-clavulanate.

MATERIALS AND METHODS

FK482 and cefixime were from Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. The other agents were obtained from their manufacturers. Fresh dilutions of compounds were prepared daily in either sterile medium or distilled water. The majority of isolates came from patients seen at The Presbyterian Hospital in New York City. Some isolates had been sent for characterization of β-lactamases. These isolates were used to determine the activity of the compound against organisms with characterized β-lactamases.

Antimicrobial activity was measured by an agar dilution method with Mueller-Hinton agar unless specified otherwise. A final inoculum of 10^4 CFU, prepared by dilution of a fresh overnight broth culture, was applied to agar with a replicating-spot device. Broth dilutions were performed with a final inoculum of 5×10^5 CFU in tubes with 1-ml volumes. Plates or tubes were incubated at 35°C for 18 h. The MIC was defined as the lowest concentration of antibiotic that inhibited development of visible growth on agar or in broth. The MBC was determined by subculture of 0.01 ml of broth in tubes without visible growth and was defined as the concentration which produced a ≥99.9% reduction in CFU after 24 h of incubation at 35°C (10). The susceptibilities of streptococci were determined by using Mueller-Hinton agar supplemented with 5% human blood. The susceptibilities of *Neisseria* and *Haemophilus* species were determined on GC agar (BBL Microbiology Systems, Cockeysville, Md.) supplemented with IsoVitaleX and hemoglobin in the presence of 5% CO_2. Anaerobic bacterial susceptibilities were determined by using brucella agar supplemented with sheep blood and vitamin K. Incubation of anaerobic bacterial cultures was for 48 h in GasPak jars (BBL).

The presence of β-lactamase in isolates was determined by the nitrocefin assay (7). β-Lactamases used for the analysis of the stability of the compounds were either purified enzymes or partially purified enzymes, as previously described (7). Stability to β-lactamase was determined by a spectrophotometric assay. Inhibition assays, with nitrocefin as the substrate, were performed with 10^{-4} M nitrocefin or cephaloridine in a final volume of 3 ml. Enzyme and FK482 at 10^{-4} or 10^{-5} M were incubated at 30°C for 10 min, and then nitrocefin or cephaloridine was added. Changes in the A_{482} for nitrocefin and the A_{265} for cephaloridine were monitored over 10 min with a temperature-controlled recording spectrophotometer. As a control, the change in the absorbance of nitrocefin plus enzyme or of cephaloridine plus enzyme was monitored.

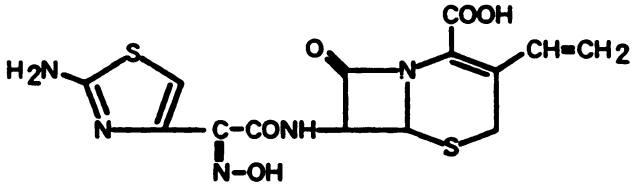

FIG. 1. Structure of FK482, (6*R*,7*R*)-7-[(*Z*)-2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

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TABLE 1. Comparative in vitro activity of FK482 against gram-positive and gram-negative organisms

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		Range	50%	90%
Staphylococcus aureus, oxacillin susceptible (29)	FK482	0.03–4	0.5	1
	Cefixime	4–64	16	32
	Cephalexin	4–16	4	8
	Cefuroxime	1–4	2	2
	Amox-clav[b]	0.5–1	1	1
Staphylococcus aureus, oxacillin resistant (13)	FK482	16–>128	32	64
Coagulase-negative staphylococci, oxacillin susceptible (23)	FK482	0.03–4	0.12	2
	Cephalexin	2–16	2	8
	Cefuroxime	0.25–2	0.5	4
	Amox-clav	0.12–8	0.5	8
Coagulase-negative staphylococci, oxacillin resistant (15)	FK482	8–128	32	128
Streptococcus pyogenes (18)	FK482	0.008–0.015	0.008	0.015
	Cefixime	≤0.015–0.25	0.06	0.25
	Cephalexin	0.12–8	0.25	2
	Cefuroxime	≤0.015–0.06	≤0.015	0.06
	Amox-clav	≤0.015–0.12	0.03	0.12
Streptococcus agalactiae (24)	FK482	0.008–0.06	0.015	0.03
	Cefixime	0.03–0.25	0.12	0.25
	Cephalexin	1–8	4	8
	Cefuroxime	≤0.05–0.12	0.03	0.12
	Amox-clav	≤0.015–0.5	0.015	0.25
Streptococcus groups C, G, and F (20)	FK482	0.015–0.03	0.015	0.03
	Cefixime	0.015–1	0.03	0.12
Viridans group streptococci (27)	FK482	0.06–8	0.5	4
	Cefixime	0.015–>128	0.5	16
	Cephalexin	0.12–>128	2	32
	Cefuroxime	0.12–8	0.5	4
	Amox-clav	0.015–0.5	0.015	0.25
Streptococcus pneumoniae (15)	FK482	0.015–0.12	0.06	0.12
	Cefixime	0.015–0.5	0.06	0.25
	Cephalexin	1–8	1	4
	Cefuroxime	0.015–0.12	0.015	0.12
	Amox-clav	0.015–0.5	0.06	0.12
Enterococcus faecalis (21)	FK482	1–64	4	8
	Cefixime	>128	>128	>128
	Cephalexin	>32	>32	>32
	Cefuroxime	>32	>32	>32
	Amox-clav	0.25–2	0.5	1
Listeria monocytogenes (16)	FK482	0.25–64	2	4
	Cefixime	>32	>32	>32
	Cephalexin	>32	>32	>32
	Cefuroxime	>32	>32	>32
	Amox-clav	0.25–2	0.5	1
Escherichia coli[c] (30)	FK482	0.12–8	0.5	2
	Cefixime	0.015–4	0.12	2
	Cephalexin	4–>32	8	32
	Cefuroxime	1–>32	8	16
	Amox-clav	2–32	16	16
Klebsiella pneumoniae[c] (20)	FK482	0.06–2	0.12	1
	Cefixime	0.015–1	0.06	0.25
	Cephalexin	4–>64	8	32
	Cefuroxime	0.25–>32	2	8
	Amox-clav	0.25–64	16	32
Klebsiella oxytoca[c] (20)	FK482	0.06–16	0.12	4
	Cefixime	0.03–16	0.12	4
	Cephalexin	4–>64	8	>64
	Cefuroxime	2–>64	2	16
	Amox-clav	1–>32	8	>32
Enterobacter aerogenes[c] (20)	FK482	0.06–>128	1	32
	Cefixime	0.5–>128	0.5	16
	Cephalexin	>128	>128	>128
	Cefuroxime	16–>32	>32	>32
	Amox-clav	2–64	64	64

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		Range	50%	90%
Enterobacter cloacae[c] (20)	FK482	0.5–>128	8	>128
	Cefixime	0.06–>128	0.12	>128
	Cephalexin	>128	>128	>128
	Cefuroxime	16–>128	>128	>128
	Amox-clav	16–128	64	64
Citrobacter freundii[c] (20)	FK482	0.25–>128	2	128
	Cefixime	0.03–>128	2	>128
	Cephalexin	>128	>128	>128
	Cefuroxime	>128	>128	>128
	Amox-clav	16–64	64	64
Citrobacter diversus (15)	FK482	0.12–4	0.12	0.25
	Cefixime	0.06–4	0.12	0.5
	Cephalexin	4–8	8	8
	Cefuroxime	1–>32	4	8
	Amox-clav	1–16	2	4
Proteus mirabilis[c] (15)	FK482	0.06–0.2	0.06	0.12
	Cefixime	≤0.015–0.06	≤0.015	≤0.015
	Cephalexin	16–>128	32	64
	Cefuroxime	1–4	2	4
	Amox-clav	0.5–8	1	8
Morganella morganii[c] (15)	FK482	0.12–32	8	32
	Cefixime	≤0.015–32	2	32
	Cephalexin	64–>128	>128	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	>32	>32	>32
Proteus vulgaris[c] (10)	FK482	0.5–64	8	64
	Cefixime	≤0.015–8	≤0.015	2
	Cephalexin	16–>128	128	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	2–>16	8	>16
Providencia rettgeri[c] (10)	FK482	0.015–>128	0.06	16
	Cefixime	≤0.015–16	0.015	1
	Cephalexin	>128	>128	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	>32	>32	>32
Providencia stuartii[c] (15)	FK482	0.015–8	0.06	4
	Cefixime	≤0.015–1	≤0.015	0.5
	Cephalexin	32–>128	64	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	8–32	>32	>32
Serratia marcescens[c] (18)	FK482	4–>128	32	>128
	Cefixime	0.03–>128	2	>128
	Cephalexin	>128	>128	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	>32	>32	>32
Pseudomonas aeruginosa[c] (30)	FK482	>128	>128	>128
	Cefixime	1–>128	64	>128
	Cephalexin	>128	>128	>128
	Cefuroxime	>32	>32	>32
	Amox-clav	>32	>32	>32
Pseudomonas cepacia (10)	FK482	>16	>16	>16
Pseudomonas maltophilia (10)	FK482	>16	>16	>16
Salmonella spp.[c] (21)	FK482	0.12–1	0.25	0.5
	Cefixime	0.03–0.5	0.06	0.25
	Cephalexin	4–16	16	16
	Cefuroxime	0.5–4	1	4
	Amox-clav	0.5–>16	4	>16
Shigella spp.[c] (24)	FK482	0.12–8	0.25	0.5
	Cefixime	0.12–1	0.25	0.5
	Cephalexin	8–32	8	16
	Cefuroxime	0.25–32	1	4
	Amox-clav	16–>16	16	>16
Aeromonas hydrophila[c] (16)	FK482	0.12–4	0.25	0.5
	Cefixime	0.12	1	4
	Cephalexin	>128	>128	>128
	Cefuroxime	0.25–8	4	8
	Amox-clav	4–>16	16	16

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TABLE 1—*Continued*

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)[a]		
		Range	50%	90%
Yersinia enterocolitica[c] (15)	FK482	0.06–1	0.5	0.5
	Cefixime	0.03–8	1	1
	Cephalexin	4–>32	32	>32
	Cefuroxime	0.5–16	4	8
	Amox-clav	0.5–>16	4	16
Haemophilus influenzae (25)	FK482	0.03–1	0.25	0.25
	Cefixime	0.12–0.25	0.12	0.12
	Cephalexin	0.12–1	0.12	8
	Cefuroxime	0.25–4	0.5	1
	Amox-clav	0.25–1	0.5	0.5
Branhamella catarrhalis (13)	FK482	0.25–1	0.5	1
	Cefixime	≤0.015–0.25	0.015	0.06
	Cephalexin	1–8	2	4
	Cefuroxime	0.25–2	0.5	1
	Amox-clav	≤0.12–0.25	0.12	0.25
Neisseria gonorrhoeae (12)	FK482	0.008–0.25	0.008	0.25
	Cephalexin	0.12–4	1	4
	Amox-clav	0.12–2	0.12	0.25
Bacteroides fragilis (21)	FK482	8–>128	32	64
	Cefixime	8–>128	16	>128
	Cephalexin	>128	>128	>128
	Cefoxitin	0.12–>16	8	>16
Other *Bacteroides* sp. (15)	FK482	>64	>64	>64
Clostridium perfringens (20)	FK482	0.25–8	1	2
	Cefixime	2	2	2
	Cephalexin	2–16	8	8
	Cefoxitin	0.5–16	4	8
Peptococcus sp. (10)	FK482	0.06–4	0.25	1
Propionibacterium acnes (8)	FK482	0.015–1	0.03	
Fusobacterium sp. (5)	FK482	0.06–1	0.25	

[a] 50% and 90%, MIC for 50 and 90% of isolates, respectively.
[b] Amox-clav, Amoxicillin-clavulanate.
[c] Ampicillin resistant.

RESULTS

The activity of FK482 is shown in Table 1. FK482 had excellent activity against *S. aureus*, inhibiting 90% of oxacillin-susceptible isolates at 1 μg/ml. It was slightly more active than cefuroxime and considerably more active than cephalexin or cefixime, which had poor activities. FK482 did not inhibit oxacillin-resistant *S. aureus*. FK482 also inhibited coagulase-negative staphylococci, which included *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Staphylococcus saprophyticus*, at ≤2 μg/ml, comparable to cefuroxime and superior to amoxicillin-clavulanate and cephalexin. Hemolytic streptococci *Streptococcus pyogenes* and *Streptococcus agalactiae* were inhibited by ≤0.03 μg/ml, as were group C, F, and G streptococci. This result was similar to the activities of cefixime, cefuroxime, and amoxicillin-clavulanate. Viridans group streptococci were less susceptible (the MIC for 90% of the strains tested was 4 μg/ml), and amoxicillin-clavulanate was the most active agent against these organisms. FK482 inhibited 90% of *Streptococcus pneumoniae* isolates at 0.12 μg/ml, similar to cefuroxime. It was twofold more active than cefixime against some isolates. None of the isolates was penicillin resistant. Unlike the other cephalosporins, FK482 inhibited 90% of *Enterococcus faecalis* isolates at 8 μg/ml and 90% of *Listeria monocytogenes* isolates at 4 μg/ml.

The activity of FK482 against members of the family *Enterobacteriaceae* varied by the species. At 2 μg/ml, FK482 inhibited 90% of *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter diversus*, *Proteus mirabilis*, *Salmonella* and *Shigella* species, *Aeromonas hydrophila*, and *Yersinia enterocolitica* isolates. Against these species FK482 had activity similar to that of cefixime and usually superior to those of cefuroxime and amoxicillin-clavulanate. It inhibited all the cephalexin-resistant (MIC, >8 μg/ml) isolates of these species. In contrast, the MICs for many *Enterobacter* species, *Citrobacter freundii*, *Morganella morganii*, *Proteus vulgaris*, *Providencia* species, and *Serratia marcescens* were ≥8 μg/ml. Although FK482 was more active than cefuroxime, cephalexin, or amoxicillin-clavulanate against these species, it was appreciably less active than cefixime, since cefixime inhibited 50% of the aforementioned isolates at ≤2 μg/ml. Like the other agents, FK482 failed to inhibit *Pseudomonas aeruginosa*.

TABLE 2. Effect of inoculum size on FK482

Organism[a]	Geometric mean MIC (μg/ml) (range) at CFU of:	
	10^5	10^7
Escherichia coli	0.25 (0.12–0.5)	0.84 (0.25–2)
Klebsiella pneumoniae	0.16 (0.03–2)	1.14 (0.06–32)
Enterobacter cloacae	3.03 (1–16)	97 (16–>128)
Citrobacter freundii	4 (0.25–64)	24.2 (8–64)
Staphylococcus aureus	0.44 (0.25–0.5)	0.76 (0.25–1)
Enterococcus faecalis	3.48 (2–4)	18.4 (8–32)

[a] For all species tested, the number of isolates was five.

TABLE 3. Comparison of MICs and MBCs of FK482

Organism (no. of isolates)	Geometric mean concn (μg/ml) (range)	
	MIC	MBC
Escherichia coli (4)	0.25 (0.12–0.5)	0.35 (0.2–1)
Klebsiella pneumoniae (5)	0.22 (0.03–1)	0.25 (0.06–2)
Enterobacter cloacae (5)	4.59 (0.5–32)	21.1 (2–64)
Citrobacter freundii (3)	0.63 (0.25–2)	3.7 (1–8)
Staphylococcus aureus (4)	1 (1–1)	2.4 (1–8)

FK482 had poor activity against *Bacteroides fragilis* (MIC for 90% of the strains tested, 64 μg/ml), and other *Bacteroides* species were also resistant. It inhibited 90% of *Clostridium perfringens* isolates at 2 μg/ml and had good activity against the few peptococci, propionibacteria, and fusobacteria tested.

FK482 inhibited 90% of *H. influenzae* and *Neisseria gonorrhoeae* isolates, which included β-lactamase-positive isolates, at 0.25 μg/ml, comparable to amoxicillin-clavulanate and cefixime. It was slightly less active against *Branhamella catarrhalis* (MIC for 90% of the strains tested, 1 μg/ml).

Effect of assay conditions. The activity of FK482 in Mueller-Hinton broth versus agar was similar for five isolates each of *S. aureus*, *E. coli*, *K. pneumoniae*, *Enterobacter cloacae*, and *C. freundii*. MICs were within twofold for assays performed on Mueller-Hinton, brain heart infusion, and nutrient agars for the aforementioned species. Similarly, the MICs did not change by more than twofold when the pH of the agar was varied from 6 to 7.5. Serum and urine did not alter the MICs or MBCs for *S. aureus*, *E. coli*, or *K. pneumoniae* (five isolates of each).

An increase in inoculum size from 10^5 to 10^7 CFU increased the MICs for all of the species tested (Table 2). The increase was largest for *Enterobacter cloacae*, *C. freundii*, and *Enterococcus faecalis*. The MBCs and MICs for *E. coli*, *K. pneumoniae*, and *S. aureus* were similar (Table 3), but the MBCs were increased by 4- to 16-fold, depending on the isolate. Similar results were obtained for two isolates each of *M. morganii*, *Serratia marcescens*, and *P. vulgaris* (data not shown).

β-Lactamase stability. The β-lactamase stability of FK482 is shown in Table 4. FK482 was not hydrolyzed by the most common plasmid β-lactamase, TEM-1, and was also stable to TEM-2. The relative rates of hydrolysis of cefaclor by these enzymes were 10 and 25, respectively. Interestingly, the chromosomal P99 Richmond-Sykes type Ia enzyme also did not appreciably hydrolyze FK482. In contrast, hydrolysis by the *P. vulgaris* enzyme that hydrolyzes cefotaxime (relative rate, 10; data not shown) was similar, and the new β-lactamase that hydrolyzes cefotaxime, TEM-3, hydrolyzed FK482. FK482 was not hydrolyzed by *S. aureus* PC-1 or a *Branhamella* β-lactamase. Both PSE-2 and OXA-2, which are similar, hydrolyzed FK482, as did the *Xanthomonas maltophilia* enzyme.

Since it has been shown that a high affinity for β-lactamase contributes to the destruction of beta-lactams, we determined the inhibition of hydrolysis, an indication of enzyme affinity, for FK482. FK482 was an excellent inhibitor of P99, the *Morganella* β-lactamase, the *Klebsiella oxytoca* K-1 enzyme, and the inducible β-lactamase of *Pseudomonas aeruginosa* (Table 5).

DISCUSSION

There has been marked progress in the development of cephalosporins in the past decade (6). A number of agents which possess an aminothiazolyl group on the β-acyl side chain have been developed as potentially orally administered drugs. The two oral cephalosporins which are available in many countries are cefuroxime axetil and cefixime. Cefixime has a superior gram-negative spectrum, but it does not inhibit *S. aureus* at readily achievable concentrations (4, 9).

FK482, which has an aminothiazolyl hydroxyimino β-acyl side chain and a C-3 vinyl group, has excellent in vitro activity against hemolytic streptococci and *Streptococcus pneumoniae* and is also extremely active against *H. influenzae* and *Branhamella catarrhalis*, comparable to cefuroxime, cefixime, and other new agents such as ceftetrame, ceftemet, ceftibuten, and cefpodoxime (U-76,252, CS-807,

TABLE 4. β-Lactamase stability of FK482

β-Lactamase	Source organism	Richmond-Sykes classification	Relative rate of hydrolysis[a]	
			FK482	Cefixime
TEM-1	*Escherichia coli*	IIIa	<0.1	<0.1
TEM-2	*Escherichia coli*	IIIa	<0.1	<0.1
SHV-1	*Klebsiella pneumoniae*	IIIa	3	<0.1
P99	*Enterobacter cloacae*	Ia	<0.1	<0.1
	Morganella morganii	Ia	<0.1	<0.1
	Proteus vulgaris	Ic	8.7	
Sabath-Abraham	*Pseudomonas aeruginosa*	Id	2.3	0.15
K1	*Klebsiella oxytoca*	IV	0.3	0.1
PSE-1	*Pseudomonas aeruginosa*	V	1.8	<0.1
PSE-2	*Pseudomonas aeruginosa*	V	41.3	3.1
PSE-3	*Pseudomonas aeruginosa*	V	<0.1	<0.1
PSE-4	*Pseudomonas aeruginosa*	V	<0.1	<0.1
OXA-2	*Pseudomonas aeruginosa*	V	20.4	
PC-1	*Staphylococcus aureus*		<0.1	<0.1
	Xanthomonas maltophilia		6.1	
TEM-3	*Escherichia coli*		15.5	12.1
	Enterobacter aerogenes		14	
	Serratia marcescens		17.6	15
	Klebsiella pneumoniae		10.9	11
	Branhamella catarrhalis		<0.1	<0.1

[a] Relative to cephaloridine as 100%.

TABLE 5. Inhibition of β-lactamases by FK482

β-Lactamase	Source organism	Richmond-Sykes classification	% Inhibition of β-lactamase hydrolysis[a]
TEM-1	*Escherichia coli*	IIIa	41.0
P99	*Enterobacter cloacae*	Ia	92.2
	Morganella morganii	Ia	100
Sabath-Abraham	*Pseudomonas aeruginosa*	Id	100
K1	*Klebsiella oxytoca*	IV	98.5
PSE-2	*Pseudomonas aeruginosa*	V	23.3
OXA-2	*Pseudomonas aeruginosa*	V	16.6
PC-1	*Staphylococcus aureus*		16.6

[a] With PSE-2, OXA-2, and PC-1, 100 μM cephaloridine was used as the substrate; with the other β-lactamases, 100 μM nitrocefin was used as the substrate.

and R-3763) (1–4, 9). However, FK482 has much better activity than cefixime, ceftetrame, and ceftemet against *S. aureus*, and its MICs are also superior to the MICs reported for cefpodoxime (1, 2, 4).

Although FK482 is highly active against many members of the family *Enterobacteriaceae*, such as *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *Salmonella* and *Shigella* species, it is not as active as cefixime or cefpodoxime against *Enterobacter*, *Morganella*, or *Providencia* species and *P. vulgaris*. It should be pointed out that none of the orally available cephalosporins inhibit *Enterobacter* spp., *C. freundii*, or *Serratia marcescens* to the extent that agents such as cefotaxime, ceftriaxone, and ceftazidime do (6).

FK482 is not destroyed by the most common plasmid β-lactamase, TEM-1, which is present in *E. coli*, *H. influenzae*, and *N. gonorrhoeae*, but it is hydrolyzed by the new β-lactamases, such as TEM-3, which hydrolyze cefotaxime and ceftazidime. Since FK482 has a very high affinity for chromosomal β-lactamases, it is reasonable to suspect that it is hydrolyzed by *Enterobacter* and *Citrobacter* enzymes at the concentrations present in the periplasmic space, as are other cephalosporins.

The in vitro activity of FK482 supports further study of its use in respiratory, soft tissue, and some urinary tract infections, depending on its pharmacological properties.

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