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In Vitro Activity and β-Lactamase Stability of U-63196E, a Novel Cephalosporin

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The in vitro activity of U-63196E, a new broad-spectrum cephalosporin antibiotic, was studied against various gram-positive and gram-negative bacteria and compared with the in vitro activities of cefotaxime, moxalactam, cefoperazone, ceftazidime, and aztreonam. Although U-63196E inhibited many ampicillin-resistant bacteria and its activity against gram-negative species was similar to cefoperazone, it was much less active than the other agents. U-63196E was less active than cefazolin against gram-positive species, and it was less active than cefoxitin or moxalactam against *Bacteroides fragilis*. U-63196E did not inhibit most cefoperazone- or cefsulodin-resistant *Pseudomonas aeruginosa*. There was a difference between minimal inhibitory concentrations and minimal bactericidal concentrations for isolates which contained β-lactamases. Plasmid β-lactamases of the TEM, HSV, OXA, and PSE types hydrolyzed U-63196E. But U-63196E was relatively stable against hydrolysis by the chromosomal β-lactamases.

Although a large number of new cephalosporins such as cefotaxime, ceftizoxime, cefoperazone, and moxalactam have been shown to have extensive in vitro antibacterial activity and clinical efficacy (4), there has been a continued search for new compounds. Studies of structure-activity relationships have demonstrated a correlation between structural properties and increased β-lactamase stability and loss of activity against certain species (1). U-63196E (Fig. 1) has a novel chemical structure unlike that present in most of the iminomethoxy cephalosporins or those which have a methoxy group on the β-lactam ring such as cefoxitin or moxalactam. Preliminary reports have suggested that U-63196E, also called AC 1370, was active in vitro against many bacteria (N. Kato, Y. Sasaki, Y. Yugari, H. Kosuzume, H. Iñaba, H. Onishi, T. Murata, M. Inove, and S. Mitsuhashi, Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami, Fla., abstr. no. 205, 1982). Therefore, we wished to compare the in vitro activity of U-63196E with other β-lactams and to establish its stability against attack by β-lactamases of both plasmid and chromosomal origin.

MATERIALS AND METHODS

Samples of U-63196E were a gift of The Upjohn Co. Antibiotics were donated by the following companies: cefamandole and moxalactam, Lilly Research Laboratories; cefoxitin, Merck Sharp & Dohme; cefotaxime, Hoechst-Roussel Pharmaceuticals, Inc.; cefoperazone, Pfizer Inc.; ceftazidime, Glaxo Inc.; and aztreonam, E. R. Squibb & Sons, Inc. Ampicillin was provided by Beecham Laboratories, and cefazolin was provided by Smith Kline & French Laboratories.

Fresh dilutions of the compounds were prepared daily in either sterile medium or distilled water. Bacterial isolates were obtained from patients hospitalized at the Columbia-Presbyterian Medical Center, New York, N.Y. In some experiments, isolates tested were known to be multiply resistant to antibiotics or to contain β-lactamases. Some isolates had been stored frozen for a number of years.

Antimicrobial activity was measured by an agar dilution method with Mueller-Hinton agar, unless specified otherwise. A final inoculum of 10^5 CFUs, prepared by dilution of a fresh overnight broth culture, was applied to agar with a replicating spot device. Broth dilutions were performed in tubes of 1-ml volume with a final inoculum of 10^5 CFU. Plates or tubes were incubated at 35°C for 18 h. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antibiotic that inhibited development of visible growth on agar or in broth. The minimal bactericidal concentration (MBC) was determined by plating 0.1-ml amounts from clear, 1-ml broth tubes onto blood agar plates. The MBC was the concentration at which there was no growth after 24 h of incubation at 35°C. Susceptibility of streptococci was determined by using Mueller-Hinton agar supplemented with 5% sheep blood. Susceptibility of *Neisseria*

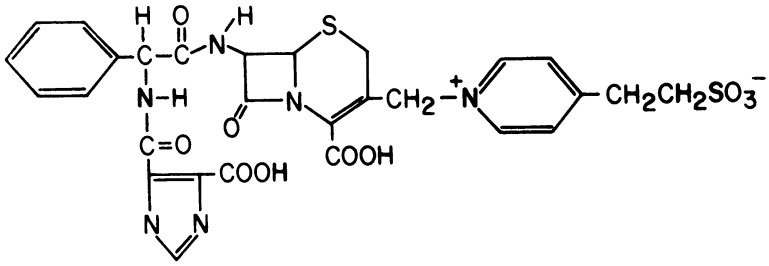

FIG. 1. Chemical structure of U-63196E, 7-β-D-(−)-α-[4(5)-carboxy-imidazole-5(4)-carboxamido]phenylacetamido-3-(4-β-sulfoethylpyridinium)methyl-3-cephem-4-carboxylic acid.

sp. and *Haemophilus* sp. was determined on chocolate Mueller-Hinton agar in the presence of 5% CO_2. Susceptibility of anaerobic bacteria was determined by using brucella agar supplemented with sheep blood and vitamin K. Incubation of anaerobic cultures was for 48 h in a GasPak jar (BBL Microbiology Systems).

Presence of β-lactamase in isolates was determined by the nitrocefin assay. β-Lactamases used for the analysis of the stability of the compounds were either purified enzymes or partially purified enzymes previously described (2, 3, 7). Stability to β-lactamase was determined by a spectrophotometric assay by using the change in absorbance at the absorption maximum of each substrate. Inhibition assays, with nitrocefin as substrate, were performed with 10^{-4} M nitrocefin or cephaloridine in a final volume of 3 ml. Enzyme and U-63196E at 10^{-4} or 10^{-5} M were incubated at 30°C for 10 min, and then nitrocefin or cephaloridine was added. Change in absorbance at 482 nm for nitrocefin and at 265 nm for cephaloridine was followed over 10 min in a temperature-controlled recording spectrophotometer. As a control, the change in the absorbance of nitrocefin plus enzyme or of cephaloridine plus enzyme was followed.

RESULTS

The comparative activity of U-63196E and other agents is shown in Table 1. Although U-63196E inhibited 50% (MIC_{50}) of *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Proteus vulgaris, Providencia* sp., *Salmonella* sp., *Serratia* sp., and *Shigella* sp. at concentrations of <12.5 μg/ml, it was much less active than the other agents tested since cefotaxime, moxalactam, ceftazidime, aztreonam, and even cefoperazone inhibited 50% of all of these species at ≤0.8 μg/ml. In each of these species, there were organisms in which the MICs for 90% of the organisms (MIC_{90}) of U-63196E were >100 μg/ml. There was a correlation of MICs with the presence or absence of β-lactamases for members of the family *Enterobacteriaceae*. Those isolates which contained β-lactamases had the higher MICs. Even considering the MIC_{50}s, U-63196E was less active than β-lactamase-stable cefotaxime, moxalactam, ceftazidine, and aztreonam. U-63196E had higher MIC_{50}s and MIC_{90}s than did cefoperazone, which is not completely β-lactamase stable against most organisms.

The activity of U-63196E against *Haemophilus influenzae* and *Neisseria gonorrhoeae*, which included strains that contained β-lactamases, was good with MICs of ≤ 0.8 μg/ml, but it was much less active than the other compounds tested. U-63196E did not inhibit *Acinetobacter* sp., and it had poor activity against *Pseudomonas cepacia* and *Pseudomonas maltophilia*, MIC_{50} of 100 μg/ml. Although the MIC_{50} of U-63196E against the carbenicillin-resistant *Pseudomonas aeruginosa* isolates was 12.5 μg/ml, aztreonam, cefsulodin, and ceftazidime were more active. A comparison of the activity of U-63196E against *P. aeruginosa* selected for resistance to carbenicillin (MIC > 200 g/ml) and gentamicin (MIC > 12.5 μg/ml) is shown in Table 2. U-63196E inhibited moxalactam-resistant isolates, but those strains with high cefoperazone, cefsulodin, and ceftazidime MICs had high U-63196E MICs or were resistant.

U-63196E was much less active than cefazolin or cefoperazone against *Staphylococcus aureus* or *Staphylococcus epidermidis*. For example, a *Staphylococcus aureus* strain with a cefazolin MIC of 0.4 μg/ml was inhibited by 25 μg of U-63196E per ml. Furthermore, U-63196E did not inhibit methicillin-resistant staphylococci or enterococci. The activity of U-63196E was considerably poorer against streptococcal species than we have reported for cefotaxime and cefoperazone (5, 6), with MIC_{50}s of 0.8 to 1.6 μg/ml. Penicillin-resistant *Streptococcus pneumoniae* and some viridans group streptococci were resistant to U-63196E.

The in vitro activity of U-63196E was also tested against a number of other species. It failed to inhibit *Alcaligenes faecalis, Clostridium difficile, Eubacterium lente, Pseudomonas diminuta, Pseudomonas fluorescens*, and a *Yer-*

TABLE 1. Comparative in vitro activity of U-63196E and other antibiotics

Organism (no. of strains)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Acinetobacter sp. (25)[a]	U-63196E	12.5->100	100	>100
	Aztreonam	0.1->100	50	>100
	Cefotaxime	0.2->100	12.5	>100
	Moxalactam	0.2->100	100	>100
	Ceftazidime	0.4->100	6.3	>100
	Cefoperazone	3.1->100	50	>100
Bacteroides fragilis (22)[a]	U-63196E	12.5->200	25	>100
	Cefoxitin	3.1-25	6.3	12.5
	Moxalactam	1.6-100	6.3	25
C. diversus (14)[a]	U-63196E	0.4-12.5	1.6	6.3
	Aztreonam	≤0.01-0.4	0.025	0.1
	Cefotaxime	0.025-0.1	0.05	0.1
	Moxalactam	0.05-0.2	0.05	0.2
	Ceftazidime	0.1-0.4	0.1	0.2
	Cefoperazone	0.1-6.3	0.1	0.4
C. freundii (24)[a]	U-63196E	1.6->100	12.5	>100
	Aztreonam	≤0.01-12.5	0.1	6.3
	Cefotaxime	0.05-50	0.2	25
	Moxalactam	0.1-12.5	0.2	6.3
	Ceftazidime	0.1->100	0.4	6.3
	Cefoperazone	0.1->100	0.8	25
	Gentamicin	0.2->100	0.2	0.4
Enterobacter aerogenes (18)[a]	U-63196E	0.8->100	3.1	>100
	Aztreonam	0.025-25	0.1	6.3
	Cefotaxime	0.05-25	0.2	6.3
	Moxalactam	0.1-6.3	0.2	6.3
	Ceftazidime	0.2-12.5	0.4	6.3
	Cefoperazone	0.8->100	0.4	6.3
	Gentamicin	0.05-12.5	0.1	0.4
Enterobacter agglomerans (4)[a]	U-63196E	1.6-100	12.5	100
Enterobacter cloacae (33)[a]	U-63196E	1.6->100	6.3	>100
	Aztreonam	0.025->100	0.1	3.1
	Cefotaxime	0.05-100	0.2	50
	Moxalactam	0.05-50	0.1	6.3
	Ceftazidime	0.05->100	0.4	12.5
	Cefoperazone	0.1->100	0.8	12.5
	Gentamicin	0.1-0.8	0.1	0.4
Escherichia coli (38)[a]	U-63196E	0.4->100	6.3	50
	Aztreonam	≤0.01-0.8	0.05	0.1
	Cefotaxime	≤0.01-3.1	0.05	0.4
	Moxalactam	0.025-0.8	0.05	0.2
	Ceftazidime	0.05-6.3	0.2	0.8
	Cefoperazone	0.01->100	0.4	25
	Gentamicin	0.1-0.8	0.2	0.4
H. influenzae (12)	U-63196E	0.1-0.4	0.1	0.4
	Aztreonam	<0.1-0.2	<0.1	0.2
	Cefotaxime	<0.1	<0.1	<0.1
	Moxalactam	<0.1	<0.1	<0.1
	Ceftazidime	<0.1-0.2	<0.1	<0.1
K. oxytoca (14)[a]	U-63196E	1.6->100	6.3	50
	Aztreonam	0.025-12.5	0.5	0.8
	Cefotaxime	0.025-12.5	0.5	0.1
	Moxalactam	0.1-12.5	0.1	0.4

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TABLE 1—*Continued*

Organism (no. of strains)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
	Ceftazidime	0.05–12.5	0.2	0.4
	Cefoperazone	0.1–>100	0.4	25
K. pneumoniae (34)[a]	U-63196E	1.6–100	3.1	50
	Aztreonam	≤0.01–0.2	0.05	0.1
	Cefotaxime	≤0.01–0.2	0.05	0.1
	Moxalactam	0.05–0.8	0.1	0.4
	Ceftazidime	0.1–1.6	0.2	0.4
	Cefoperazone	0.1–>100	0.4	25
	Gentamicin	0.2–>100	0.2	0.4
M. morganii (16)[a]	U-63196E	3.1–>100	6.3	100
	Aztreonam	≤0.01–0.8	0.01	0.2
	Cefotaxime	0.025–6.3	0.1	3.1
	Moxalactam	0.1–0.4	0.2	0.2
	Ceftazidime	0.05–1.6	0.1	1.6
	Cefoperazone	0.2–25	0.8	6.3
N. gonorrhoeae (11)[a]	U-63196E	0.1–1.6	<0.4	0.8
	Aztreonam	<0.05–0.2	<0.05	0.1
	Cefotaxime	<0.05–0.1	<0.05	0.1
	Moxalactam	<0.05–0.1	<0.05	0.1
	Ceftazidime	<0.05–0.2	<0.05	0.1
Proteus mirabilis (19)	U-63196E	0.2–12.5	0.2	3.1
	Aztreonam	≤0.01–0.01	≤0.01	0.01
	Cefotaxime	≤0.01	≤0.01	≤0.01
	Moxalactam	≤0.01–0.2	≤0.01	≤0.01
	Ceftazidime	0.05–0.2	0.5	0.1
	Cefoperazone	0.1–>100	0.8	1.6
Proteus vulgaris (10)[a]	U-63196E	0.2–>100	100	>100
	Aztreonam	≤0.01–0.8	0.01	0.1
	Cefotaxime	≤0.01–50	0.05	25
	Moxalactam	0.05–12.5	0.1	0.2
	Ceftazidime	0.05–50	0.1	0.8
	Cefoperazone	0.2–50	0.8	1.6
Providencia rettgeri (6)[a]	U-63196E	12.5–>100	50	>100
	Aztreonam	0.025–0.8	0.05	0.8
	Cefotaxime	0.05–1.6	0.4	1.6
	Moxalactam	0.05–0.2	0.05	0.1
	Ceftazidime	0.2–3.1	0.8	1.6
	Cefoperazone	0.2–3.1	0.4	1.6
Providencia stuartii (27)[a]	U-63196E	0.2–>100	12.5	100
	Aztreonam	≤0.01–>100	≤0.01	0.05
	Cefotaxime	≤0.01–0.8	0.05	0.2
	Moxalactam	0.05–0.5	0.05	0.2
	Ceftazidime	0.1–12.5	0.2	0.8
	Cefoperazone	0.2–>100	1.6	25
	Gentamicin	0.8–12.5	0.8	6.3
Pseudomonas aeruginosa (59)[a]	U-63196E	1.6–>100	12.5	100
	Aztreonam	0.2–>100	6.3	25
	Cefotaxime	0.4–>100	25	100
	Moxalactam	3.1–>100	12.5	100
	Ceftazidime	0.8–100	1.6	25
	Cefoperazone	0.4–>100	6.3	100
	Cefsulodin	0.4–>100	3.1	25
	Carbenicillin	>100	>100	>100
	Gentamicin	3.1–>100	6.3	>100

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TABLE 1—*Continued*

Organism (no. of strains)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
Pseudomonas cepacia (19)[a]	U-63196E	3.1–>100	100	>100
	Aztreonam	1.6–>100	6.3	25
	Cefotaxime	1.6–>100	12.5	100
Pseudomonas maltophilia (13)[a]	U-63196E	>100	>100	>100
	Aztreonam	6.3–>100	50	>100
	Cefotaxime	25–>100	100	>100
	Moxalactam	6.3–100	25	50
	Ceftazidime	1.6–>100	50	>100
Salmonella sp. (21)[a]	U-63196E	0.8–>100	6.3	>100
	Aztreonam	0.05–0.2	0.05	0.1
	Cefotaxime	≤0.01–0.8	0.05	0.2
	Moxalactam	0.1–0.4	0.1	0.2
	Ceftazidime	0.2–12.5	0.8	6.3
	Cefoperazone	0.4–>100	0.4	>100
Serratia liquefaciens (4)[a]	U-63196E	6.3–>100	6.3	>100
Serratia marcescens (34)[a]	U-63196E	0.8–>100	100	>100
	Aztreonam	0.05–12.5	0.1	3.1
	Cefotaxime	0.1–100	3.1	25
	Moxalactam	0.1–50	1.6	25
	Ceftazidime	0.1–12.5	0.8	3.1
	Cefoperazone	0.2–>100	1.6	>100
	Gentamicin	0.4–>100	3.1	>100
Shigella sp. (23)[a]	U-63196E	1.6–>100	3.1	>100
	Aztreonam	0.025–0.1	0.025	0.1
	Cefotaxime	≤0.01–0.2	0.025	0.1
	Moxalactam	0.1–0.4	0.1	0.2
	Ceftazidime	0.1–6.3	0.2	1.6
	Cefoperazone	0.1–>100	0.2	3.1
Listeria sp. (12)	U-63196E	25–>100	50	50
	Ampicillin	0.8–6.3	0.8	1.6
Staphylococcus aureus (22)[a,b]	U-63196E	25–>100	50	>100
	Methicillin	3.1–>100	6.3	25
	Cefazolin	0.2–>100	1.6	25
	Cefoperazone	0.1–>100	0.8	25
Staphylococcus epidermidis (23)[a,b]	U-63196E	6.3–>100	50	>100
	Methicillin	3.1–>100	6.3	>100
	Cefazolin	0.1–>100	0.8	12.5
	Cefoperazone	0.1–100	0.8	12.5
Streptococcus faecalis (16)	U-63196E	>100	>100	>100
	Ampicillin	0.8–3.1	1.6	3.1
Streptococcus pneumoniae (4)[c]	U-63196E	0.8–>100	0.8	>100
Streptococcus pyogenes (4)	U-63196E	0.2–3.1	0.8	3.1
Streptococcus bovis (4)	U-63196E	0.4–3.1	1.6	3.1
Streptococcus mitis (4)	U-63196E	1.6–3.1	1.6	3.1
Streptococcus agalactiae (4)	U-63196E	0.8–3.1	0.8	3.1
Viridans group streptococci (4)	U-63196E	3.1–>100	12.5	>100

[a] Isolates were resistant to ampicillin (MIC >100 μg/ml).
[b] Six isolates were methicillin resistant.
[c] Two isolates were penicillin resistant.

TABLE 2. Comparative activity of U-63196E against selected *Pseudomonas aeruginosa* isolates

P. aeruginosa isolate	MIC (μg/ml) of following antibiotic:				
	U-63196E	Cefoperazone	Cefsulodin	Moxalactam	Ceftazidime
1	50	12.5	3.1	100	6.3
4	12.5	1.6	3.1	100	12.5
11	>100	1.6	1.6	100	6.3
15	3.1	1.6	0.8	12.5	1.6
25	>100	>100	50	>100	1.6
29	12.5	3.1	12.5	50	6.3
36	6.3	3.1	3.1	6.3	1.6
5267	>100	>100	>100	50	12.5
5392	50	100	25	100	12.5
5432	25	3.1	0.8	6.3	0.8
5434	12.5	100	12.5	25	3.1
5512	25	6.3	3.1	12.5	1.6
6027	25	12.5	6.3	12.5	6.3
6583	50	>100	6.3	100	6.3

sinia enterocolitica strain, which contained a TEM-1 β-lactamase, all of which had a U-63196E MIC of > 100 μg/ml. *Klebsiella ozaenae* (MIC, 6.3 μg/ml), *Pseudomonas stuzteri* (MIC, 1.6 μg/ml), and *Aeromonas* sp. (three isolates; MIC, 3.1 μg/ml) were inhibited.

Effect of test conditions. Five isolates of *E. coli, Klebsiella* sp., *Serratia* sp., *Pseudomonas* sp., and *Staphylococcus aureus* were assayed in Mueller-Hinton, nutrient, brain heart, and Trypticase soy agar (BBL Microbiology Systems). There was no major difference in MICs. The effect of inoculum size on MICs and MBCs of U-63196E is shown for representative organisms from the 30 tested (Table 3). Although there was little difference between MICs and MBCs in inoculum sizes of 10^3 and 10^5 CFU, at 10^7 CFU for *E. coli* and *Klebsiella pneumoniae*, which were producers of the TEM β-lactamase, and for *Morganella* sp., both MICs and MBCs were markedly increased. For strains of *Escherichia coli, Enterobacter aerogenes, K. pneumoniae, Serratia marcescens, P. aeruginosa, Providencia* sp., *Citrobacter diversus*, and *Citrobacter freundii*, which were susceptible to U-63196E, MBCs were generally identical or twofold greater than MICs (Table 4).

Effect of permeability on activity. The in vitro activity of U-63196E was determined against a series of permeability mutants of *Escherichia coli* to determine the contribution that entry into the bacterial cell had on MICs. The MICs in the mutants were within one dilution or were identical to the MICs of the parent strain, indicating that poor permeability did not contribute significantly to the lower activity of U-63196E.

β-Lactamase stability. The β-lactamase stability of U-63196E was greater than that of cefoperazone, but markedly less than that of cefotaxime, cefoxitin, and moxalactam (Table 5). U-63196E was hydrolyzed by the most common plasmid-mediated β-lactamases, TEM-1, TEM-2, HSV-1, and also by OXA-1. Stability of U-63196E against the Richmond type 1a enzymes

TABLE 3. Effect of inoculum size on the MICs and MBCs of U-63196E

Organism	MICs and MBCs (μg/ml) for following inoculum size:					
	10^7		10^5		10^3	
	MIC	MBC	MIC	MBC	MIC	MBC
Enterobacter cloacae[a]	200	>200	6.3	6.3	1.6	3.1
Escherichia coli	1.6	1.6	0.8	1.6	0.4	1.6
Escherichia coli[a]	25	>200	6.3	25	1.6	6.3
K. pneumoniae	3.1	12.5	3.1	6.3	0.8	1.6
K. pneumoniae[a]	25	>200	6.3	25	1.6	6.3
M. morganii[a]	>200	>200	100	100	1.6	12.5
Proteus mirabilis[a]	200	200	0.8	1.6	0.8	1.6
Pseudomonas aeruginosa	3.1	>200	1.6	6.3	1.6	6.3
S. marcescens	1.6	6.3	0.8	1.6	0.4	0.8

[a] β-Lactamase-producing strains.

TABLE 4. Relation of U-63196E MICs and MBCs

Organism	No. tested	MBC/MIC ratio at the following multiplication:			
		1	2	4	8
Escherichia coli	23	13	8		2
Pseudomonas aeruginosa	25	13	7	4	1
Enterobacter cloacae	18	14	3		1
Enterobacter aerogenes	10	2	3	4	1
K. pneumoniae	11	6	4		1
Providencia sp.	20	5	7	4	4
C. diversus	14	5	7		2
C. freundii	23	14	7	1	1
Serratia marcescens	9	5	1	3	

in *Enterobacter* sp. and *Serratia* sp. was much greater as was its stability to a cefoxitin-induced β-lactamase of *Enterobacter cloacae*. The MICs of U-63196E correlated with the lesser β-lactamase stability since the MICs for *Escherichia coli* containing the TEM-1, TEM-2, and OXA-3 types were >100 μg/ml, as were the MICs for *Enterobacter aerogenes* containing the K-1 enzyme and *Pseudomonas aeruginosa* isolates containing PSE-1, PSE-2, PSE-3, and PSE-4. Stability of the compound to a β-lactamase of *Proteus vulgaris*, which can hydrolyze the iminomethoxy cephalosporins such as cefotaxime, was relatively good.

U-63196E was not an efficient inhibitor of the hydrolysis of nitrocefin, even when present in equimolar concentrations. This is in contrast to the effective inhibition by the iminomethoxy cephalosporins and by moxalactam of β-lactamases, which function primarily as cephalosporinases, as we have shown previously (2, 4).

DISCUSSION

U-63196E has a unique chemical structure unrelated to the iminomethoxy cephalosporins or to older cephalosporin agents. This study shows that this compound has an antibacterial activity against multiply resistant β-lactamase-producing strains similar to the activity of cefoperazone. Both compounds are not active against organisms which contain the common TEM plasmid-mediated β-lactamase when the enzyme is present in large amounts (4, 6). Furthermore, even though U-63196E is relatively stable against hydrolysis by the chromosomal cephalosporinases of many members of the family *Enterobacteriaceae* and *Pseudomonas* sp., it is much less active than cefotaxime, ceftazidime, moxalactam, and aztreonam.

U-63196E has lost appreciable gram-positive activity and actually is less active against staphylococci and streptococci than is moxalactam (4), which is the least active of the new agents against these species.

In view of these findings, it is difficult to see the precise role for this agent in the chemotherapy of serious infections. Although the compound is quite active against susceptible members of the family *Enterobacteriaceae* and has MICs comparable to those of cefamandole and cefuroxime, it fails to inhibit organisms readily inhibited by cefotaxime, ceftazidime, and moxalactam. Finally, U-63196E does not offer a major advance in antipseudomonas activity since ceftazidime and aztreonam inhibit organisms resistant to cefoperazone and cefsulodin, whereas U-63196E does not.

It may be possible that U-63196E will prove to be clinically useful since animal experiments suggest that it is more effective in animal infec-

TABLE 5. β-Lactamase stability of U-63196E

β-Lactamase type	Source[a]	Relative rate of hydrolysis for following antibiotic[b]:					
		U-63196E	Cefoperazone	Cefoxitin	Cefotaxime	Ceftazidime	Moxalactam
TEM-1	*Escherichia coli* (P)	17.5	49.2	0	0	0	0
TEM-2	*Escherichia coli* (P)	52.5	42	0	0	0	0
OXA-2	*Escherichia coli* (P)	40	56	0	0	0	0
HSV-1	*Klebsiella* sp. (P)	40	71	0	0	0	0
PSE-1	*Pseudomonas* sp. (P)	72	12.6	0	0	0	0
P99	*Enterobacter* sp. (C)	15.8	8.4	0	0	0	0
	Morganella (C)	17.2	8.5	0	0	0	0
	Proteus vulgaris (C)	15.2	8.4	0	42	3	0
	Serratia sp. (C)	5.8	14.7	0	0	0	0
	Enterobacter cloacae (C)[c]	10.7	3.2	0	2	0	0
	Bacillus cereus (C)[d]	24.8	6.7	0	0	0	0

[a] P, Plasmid; C, chromosomal.
[b] Based on hydrolysis of cephaloridine equal to 100.
[c] Cefoxitin-induced enzyme.
[d] Zn-stimulated enzyme.

tions than would be predicted by the MICs (22nd ICAAC, abstr. no. 205).

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