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In Vitro Activity of Cefodizime (HR-221)

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The in vitro activity of cefodizime (HR-221), a new cephalosporin antibiotic, was compared with the activities of selected antimicrobial agents against a broad spectrum of aerobic bacteria. Cefodizime concentrations of 2 μg/ml inhibited about 90% of *Enterobacteriaceae* studied. *Serratia marcescens* required 8 μg/ml to inhibit 90% of strains. Among gram-positive cocci, 50% of strains were inhibited by 2 μg/ml of cefodizime (including methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, and penicillin-resistant *Streptococcus pneumoniae*). *Pseudomonas aeruginosa* was less susceptible to cefodizime. Cefotaxime, an antibiotic closely related to cefodizime structurally, was about fourfold more active.

Newer cephalosporin derivatives such as cefotaxime, cefmenoxime, cefuroxime, and ceftriaxone have a methoxyimino group in the 7 position which confers on them resistance to most β-lactamases (3).

Cefodizime (HR-221), a new cephalosporin antibiotic synthesized by Hoechst AG, is similar to these antimicrobial agents, and its mercaptothiazol substitute at the 3 position leads to longer serum half-life in experimental animals (P. Hajdu, N. Klesel, B. Mencke, J. Reden, E. Schrinner, K. Seeger, and G. Seibert, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 117, 1981). We report the in vitro antibacterial activity of cefodizime against a broad spectrum of aerobic bacteria, including the *Enterobacteriaceae* and several species of gram-positive cocci.

Standard powders of the following antibiotics were used: cefodizime, cefotaxime (Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.), moxalactam, cephalothin (Eli Lilly Research Laboratories, Indianapolis, Ind.), cefoperazone (Pfizer Inc., New York, N.Y.), gentamicin (Schering Corp., Bloomfield, N.J.), and ampicillin and oxacillin (Beecham Laboratories, Bristol, Tenn.).

The bacterial strains examined totaled 566 and consisted of clinical isolates randomly chosen from the Jewish Hospital and Medical Center of Brooklyn, the Kings County Hospital Center, and the State University Hospital between 1979 and 1981. A few strains (penicillin-resistant pneumococci) were obtained from research laboratories. There were no β-lactamase-producing strains of *Haemophilus influenzae*. All organisms had been preserved by freezing at −70°C and thawed only once for susceptibility testing.

Antimicrobial activity was measured as minimal inhibitory concentrations (MICs), using a broth microdilution method. MICs were determined as previously described, using an automatic dispenser and inoculator (MIC 2000, Dynatech Laboratories, Inc., Alexandria, Va.) with an inoculum of about 10^5 colony-forming units per ml (1). For minimal bactericidal concentration (MBC) determination, Mueller-Hinton agar plates were inoculated with samples (0.015 ml) of final inoculum-antibiotic mixtures from each well. MBC was defined as the lowest concentration of antibiotic that supported no growth after 18 to 24 h of incubation at 37°C.

The activity of cefodizime compared with the activities of other antimicrobial agents against various bacterial species is shown in Table 1. Although cefotaxime and cefodizime had very good activities against the *Enterobacteriaceae*, cefotaxime was overall more than fourfold more active. At a concentration of ≤2 μg/ml, cefodizime inhibited 87% of *Enterobacteriaceae*, and at ≤8 μg/ml, it inhibited 100%. Cephalothin, with MICs active against 90% (MIC_{90}) and 100% of strains of ≤8 and ≥64 μg/ml, respectively, against the *Enterobacteriaceae*, was considerably less active. Thus, cefodizime was at least four to eight times more active than cephalothin. The activities of moxalactam and cefoperazone were generally comparable to the activity of cefodizime. *Pseudomonas aeruginosa* had lower susceptibility to cefodizime and the other cephalosporin derivatives tested.

Methicillin-susceptible *Staphylococcus aureus* was four times more susceptible to oxacillin (MIC_{90} = 0.5 μg/ml) than to cefodizime (MIC_{90}

TABLE 1. Comparative activities of cefodizime and other antimicrobial agents against selected organisms

Organism (no. tested)	Drug[a]	MIC (μg/ml)		MBC (μg/ml)	
		Range	90%	Range	90%
Escherichia coli (40)	CDZ	0.06–0.5	0.25	0.06–0.5	0.25
	CFT	≤0.01–0.125	0.03	≤0.01–0.125	0.03
	MXL	0.03–0.25	0.125	0.03–0.25	0.125
	CPZ	≤0.01–4	2	≤0.01–4	2
	CFL	1–32	8	1–32	8
Klebsiella pneumoniae (40)	CDZ	0.125–0.25	0.25	0.125–0.25	0.25
	CFT	≤0.01–0.06	0.03	≤0.01–0.06	0.03
	MXL	0.06–0.5	0.125	0.06–0.5	0.5
	CPZ	0.06–4	2	0.06–4	2
	CFL	1–8	8	1–8	8
Proteus mirabilis (40)	CDZ	≤0.01–0.06	0.3	≤0.01–0.06	0.3
	CFT	≤0.01–0.06	0.03	≤0.01–0.06	0.03
	MXL	0.03–0.25	0.125	0.03–0.25	0.125
	CPZ	0.125–0.5	0.5	0.125–0.5	0.5
	CFL	2–8	8	2–8	8
Providencia stuartii (22)	CDZ	0.06–4	0.5	0.06–4	0.5
	CFT	≤0.01–0.5	0.05	≤0.01–0.5	0.25
	MXL	0.03–0.5	0.5	0.03–0.5	0.5
	CPZ	0.5–8	8	0.5–8	8
	CFL	8–16	16	8–16	16
Morganella morganii (40)	CDZ	≤0.01–2	0.5	≤0.01–2	0.5
	CFT	≤0.01–0.03	0.03	≤0.01–0.03	0.03
	MXL	0.06–0.5	0.25	0.06–0.5	0.25
	CPZ	0.125–8	1	0.125–8	1
	CFL	8–16	16	8–16	16
Enterobacter cloacae (40)	CDZ	0.06–2	2	0.06–2	2
	CFT	≤0.01–0.5	0.25	≤0.01–0.5	0.25
	MXL	0.03–2	2	0.03–2	2
	CPZ	0.125–8	0.5	0.125–8	0.5
	CFL	4–16	16	4–16	16
Serratia marcescens (40)	CDZ	0.25–64	8	0.25–64	8
	CFT	0.06–2	1	0.06–2	1
	MXL	0.125–4	2	0.125–4	2
	CPZ	0.5–8	8	0.5–8	8
	CFL	8–≥64	≥64	8–≥64	≥64
Pseudomonas aeruginosa (40)	CDZ	16–≥64	≥64	16–≥64	≥64
	CFT	4–≥64	≥64	4–≥64	≥64
	MXL	4–≥64	≥64	4–≥64	≥64
	CPZ	8–≥64	≥64	8–≥64	≥64
	GENT	0.125–4	1	0.125–4	1
Salmonella spp. (27)	CDZ	≤0.01–1	0.5	≤0.01–1	0.5
	CFT	≤0.01–0.03	0.03	≤0.01–0.03	0.03
	MXL	0.03–0.25	0.125	0.03–0.25	0.125
	CPZ	0.125–0.5	0.5	0.125–0.5	0.5
Shigella sonnei (13)	CDZ	0.06–0.25	0.25	0.06–0.25	0.25
	CFT	≤0.01–0.03	0.03	≤0.01–0.03	0.03
	MXL	0.06–0.5	0.25	0.06–0.5	0.25
	CFPZ	0.25–16	16	0.25–16	16
Haemophilus influenzae (ampicillin susceptible) (20)	CDZ	≤0.01–0.125	0.125	≤0.01–0.125	0.125
	CFT	≤0.01–0.25	0.125	≤0.01–0.25	0.125
	MXL	0.03–0.5	0.5	0.03–0.5	0.5
	AMP	0.125–0.5	0.5	0.125–0.5	0.5

TABLE 1—*Continued*

Organism (no. tested)	Drug[a]	MIC (μg/ml)		MBC (μg/ml)	
		Range	90%	Range	90%
Neisseria gonorrhoeae (5)	CDZ	0.125–0.25	0.25	0.125–0.25	0.25
	CFT	≤0.01–0.125	0.125	≤0.01–0.125	0.125
	MXL	0.06–0.125	0.125	0.06–0.125	0.125
	AMP	0.125	0.125	0.125	0.125
Yersinia enterocolitica (7)	CDZ	0.125	0.125	0.125	0.125
	CFT	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	MXL	0.125	0.125	0.125	0.125
	GENT	0.5–1	1	0.5–1	1
Listeria monocytogenes (11)	CDZ	32–≥64	≥64	32–≥64	≥64
	CFT	8	8	≥64	≥64
	MXL	32–≥64	≥64	≥64	≥64
	CPZ	8–16	16	≥64	≥64
	AMP	0.125–0.5	0.5	16–≥64	≥64
Staphylococcus aureus (methicillin susceptible) (20)	CDZ	0.5–2	2	0.5–2	2
	CFT	0.25–2	1	0.25–2	1
	MXL	0.25–8	8	0.25–8	8
	OX	0.125–1	0.5	0.125–1	0.5
Staphylococcus aureus (methicillin resistant) (32)	CDZ	8–≥64	≥64	8–≥64	≥64
	CFT	8–≥64	≥64	8–≥64	≥64
	MXL	32–≥64	≥64	32–≥64	≥64
	OX	32–≥64	≥64	32–≥64	≥64
Staphylococcus epidermidis (30)	CDZ	0.5–≥64	≥64	0.5–≥64	≥64
	CFT	0.06–≥64	≥64	0.06–≥64	≥64
	MXL	1–≥64	≥64	1–≥64	≥64
	OX	0.125–≥64	≥64	0.125–≥64	≥64
Streptococcus faecalis (29)	CDZ	4–≥64	≥64	4–≥64	≥64
	CFT	4–≥64	≥64	4–≥64	≥64
	MXL	4–≥64	≥64	4–≥64	≥64
	AMP	0.5–1	1	1	1
Streptococcus pneumoniae (oxacillin susceptible) (10)	CDZ	0.06–0.125	0.06	0.06–0.125	0.06
	CFT	≤0.01–0.06	0.03	≤0.1–0.06	0.03
	MXL	0.125–1	0.5	0.125–1	0.5
	AMP	0.03–0.125	0.125	0.03–0.125	0.125
Streptococcus pneumoniae (oxacillin resistant) (10)	CDZ	0.5–2	1	0.5–2	1
	CFT	0.5–1	1	0.5–1	1
	MXL	1–8	4	1–8	4
	AMP	2–8	8	2–8	8
Streptococcus pyogenes (11)	CDZ	0.03–0.125	0.06	0.03–0.125	0.06
	CFT	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	MXL	1–4	4	1–4	4
	AMP	0.03–0.125	0.125	0.03–0.125	0.125
Streptococcus agalactiae (8)	CDZ	0.03–0.125	0.06	0.03–0.125	0.06
	CFT	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	MXL	1–4	4	1–4	4
	AMP	0.03–0.125	0.125	0.03–0.125	0.125
Other *Streptococcus* spp.[b] (beta-hemolytic) (14)		0.06–0.125	0.06	0.06–0.125	0.06
	CFT	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	MXL	1–4	4	1–4	4
	AMP	0.03–0.25	0.25	0.03–0.25	0.25

TABLE 1—*Continued*

Organism (no. tested)	Drug[a]	MIC (μg/ml)		MBC (μg/ml)	
		Range	90%	Range	90%
Streptococcus viridans group (17)	CDZ	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	CFT	≤0.01–0.06	0.06	≤0.01–0.06	0.06
	MXL	0.25–1	1	0.25–1	1
	AMP	≤0.01–0.125	0.125	≤0.01–0.125	0.125

[a] CDZ, cefodizime; CFT, cefotaxime; MXL, moxalactam; CPZ, cefoperazone; CFL, cephalothin; GENT, gentamicin; AMP, ampicillin; OX, oxacillin.
[b] Includes *Streptococcus* groups C and G.

= 2 μg/ml) and the other cephalosporins tested. Methicillin-resistant *S. aureus* and *S. epidermidis* were resistant to cefodizime (MIC_{90} = 64 μg/ml). Streptococci were quite susceptible to cefodizime (MIC_{90} ≤ 0.06 μg/ml), with the clear exception of *Streptococcus faecalis*, which was uninhibited by 64 μg/ml. Compared with ampicillin, cefodizime was twice to four times more active against susceptible *Streptococcus* spp.

Cefodizime (HR-221) was more active against *Enterobacteriaceae* than was cephalothin, about as active as moxalactam and cefoperazone, and less active than cefotaxime in this study. It had relatively little activity against *P. aeruginosa*. These findings are generally consistent with reports published by Jones et al. (2) and other investigators (W. Stille, S. Spieler, and P. M. Shah, 21st ICAAC, abstr. no. 118). Jones et al. reported cefodizime MIC_{90} values of 4, 8, and 32 μg/ml against *Morganella morganii, Providencia* spp., and *Enterobacter* spp., respectively. Our lower MIC_{90} values of 0.5, 0.5, and 2 μg/ml for the same group of bacteria may in part be because we studied only single species, whereas the previous authors tested multiple species within the genera *Providencia* and *Enterobacter*, or because of local differences in susceptibility. Cefodizime was also quite active against gram-positive cocci, a finding which is in accord with previous data (G. Seibert, W. Durckheimer, N. Klesel, M. Limbert, E. Schrinner, K. H. Schennemann, and K. Seegen, 21st ICAAC, abstr. no. 116). However, this activity is lower than that of nafcillin. *S. faecalis, S. epidermidis*, and methicillin-resistant *S. aureus* were, however, all resistant to cefodizime, the MIC_{90} being ≥64 μg/ml. Several potential β-lactamase-producing species, such as *H. influenzae* and *Neisseria gonorrhoeae*, were also very susceptible to cefodizime.

These in vitro data indicate that cefodizime appears to be more active than a first-generation cephalosporin, cephalothin, but is relatively less active than some third-generation cephalosporins. Despite its longer half-life, its potential clinical utility would be limited due to its relatively intermediate order of activity.

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