Cefoxitin, a Semisynthetic Cephamycin Antibiotic: Antibacterial Spectrum and Resistance to Hydrolysis by Gram-Negative Beta-Lactamases

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Received for publication 4 April 1974

The in vitro activity of cefoxitin, 3-carbamolyloxymethyl-7- α -methoxy-7 [2-(2-thienyl)acetamido]-3-cephem-4-carboyxlic acid, was investigated. Activity against gram-positive organisms was less than that of cephalothin and cephloridine. It was highly active against gram-negative bacilli, with activity against Escherichia coli, Proteus mirabilis, and Klebsiella pneumoniae equal to that of currently available cephalosporins. In addition, it was active against certain Enterobacter strains, Serratia marcescens, indole-positive Proteae and Herellea. The strains of these latter bacteria were strains susceptible to carbenicillin and ticarcillin. Pseudomonas aeruginosa and other Pseudomonas species were resistant. Changes in pH, inoculum size, and type of growth medium had no significant effect on the activity of the antibiotic. Cefoxitin was highly resistant to hydrolysis by various types of gram-negative beta-lactamases. The precise role of resistance to beta-lactamase hydrolysis varied from strain to strain. Bacterial resistance to cefoxitin was not necessarily related to hydrolysis of the antibiotic. However, the resistance of cefoxitin to hydrolysis did contribute to its activity. Cefoxitin could function as an inducer of beta-lactamase activity and effectively bound to purified beta-lactamases.

Cephalosporin antibiotics currently available for clinical use in the United States have an important role in the treatment of many serious infections caused by both gram-positive and gram-negative bacteria. There are certain members of the Enterobacteriaceae, such as Enterobacter, Serratia, and indole-positive Proteae species, that are consistently resistant to agents such as cephalothin, cephaloridine, and cefazolin. Cefoxitin, a semisynthetic cephamycin analogue, is a new cephalosporin-like antibiotic that has unique activity against some gram-negative strains (2, 9, 11). This paper reports studies of the overall antibacterial activity of cefoxitin in comparison with cephalosporin antibiotics and investigates the resistance of cefoxitin to hydrolysis by beta-lactamase-containing bacteria.

MATERIALS AND METHODS

Cefoxitin was obtained from Merck Sharp & Dohme Research Laboratories. Cephalothin, cephloridine, and cephalexin were gifts from Eli Lilly & Co. Ampicillin, carbenicillin, and ticarcillin were gifts from Beecham-Massengill Pharmaceuticals. Bacterial strains were isolates from patients hospitalized at the Columbia-Presbyterian Medical Center, New York City.

Susceptibility testing methods. The activity of cefoxitin was measured by a microtiter broth dilution technique. Serial twofold dilutions in brain-heart infusion broth (Difco) were used with an inoculum of 10⁴ colony-forming organisms (CFU) from an overnight culture. Incubation was for 18 h at 35 C. The minimal inhibitory concentration (MIC) of antibiotic was defined as the lowest concentration that inhibited development of visible turbidity. The minimal bactericidal concentration was determined by plating clear wells from the microtiter plates. MIC values were also determined by the agar-dilution method with Mueller-Hinton agar. A 100-fold dilution of an overnight culture was applied with a replicating device.

Assay for antibiotic. Filter paper disks were dipped in test solutions and placed on brain-heart infusion agar seeded with Staphylococcus aureus. Zones of inhibition were measured with calipers, and concentration of antibiotic was determined from curves constructed from plots of standards run in an identical manner.

Beta-lactamase preparations. Purified beta-lactamases prepared by published methods (5, 7, 10) were used in some experiments. Crude beta-lactamase preparations were made by subjecting strains to sonic disruption and by using as enzyme the supernatant material from a high-speed centrifugation.

Assays of beta-lactamase. Hydrolysis of cefoxitin and other cephalosporin antibiotics was performed wih either a microiodometric modification of the

Novick method (8) or with purified enzymes by utilizing a spectrophotometric method (5).

Induction of beta-lactamase. Bacterial strains were grown in brain-heart infusion broth in side-arm flasks to a density of 10° CFU. Antibiotics were added in concentrations specified for each experiment. Induction was continued for 3 to 6 h, and organisms were removed by centrifugation. Bacteria were washed with room temperature, 0.05 M, pH 7.0, potassium phosphate buffer and then were resuspended in broth for studies with intact organisms or were sonically disrupted with a Branson sonifier. Growth of organisms was followed with a Klett spectrophotometer.

RESULTS

Cefoxitin is much less effective than are most cephalosporins against the common gram-positive coccal organisms; the MIC of cefoxitin for S. aureus was from 1.6 to 6.4 μ g/ml, with 86% inhibited by 3.2 μ g/ml (Table 1). This could be contrasted to an average cephalothin inhibitory concentration of 0.4 μ g/ml, but is quite comparable to the 3.2 μ g/ml cephalexin MIC for S. aureus (3). Cefoxitin showed greater activity

against streptococci and pneumococci than it did against the staphylococci, but in general the activity was similar to that of cephalexin and less than that achieved with other cephalosporips

Cefoxitin was active against a wide range of gram-negative organisms (Table 2). Indeed, only Pseudomonas species can be said to be uniformly resistant. Escherichia coli showed a fairly uniform susceptibility, with 35% susceptible to 3.1 μ g/ml and 73% to 6.25 μ g/ml. Cefoxitin at a concentration of 6.25 µg/ml inhibited 74% of Proteus mirabilis strains. Most Salmonella and Shigella species were susceptible to 1.6 µg/ml. Most Proteus rettgeri were susceptible to 25 μ g/ml or less, and *Proteus* morganii and Proteus vulgaris were inhibited by 12.5 to 25 μg/ml. Activity against Enterobacter species was variable. The majority of strains tested were resistant. Enterobacter aerogenes was the most readily inhibited of the four species. Serratia marcescens strains also showed a variable resistance pattern. The strains had been bacteriocin typed to avoid a

TABLE 1. Cumulative number of gram-positive isolates susceptible to cefoxitin

Organism	No. of	No. susceptible at MIC (µg/ml) of:							
Organism	isolates	<0.8	0.8	1.6	3.2	6.4	12.5	25	>25
Staphylococcus aureus	10 10 10	5 3	1 4 6	8 4 1 1	12 5	3			
Streptococcus faecalis			1	2	4	1	1	1	10

Table 2. Cumulative number of gram-negative isolates susceptible

Ownerious	No. of	No. susceptible at MIC (µg/ml) of:								
Organism	isolates	0.8	1.63	3.12	6.25	12.5	25	50	100	>100
Escherichia coli	89	2	8	22	33	19		3		2
Proteus mirabilis	55	1	2	18	20	7	3	2		2
Proteus vulgaris	16				3	5	2	1	1	4
Proteus morganii	32				1	7	12	8	2	2
Proteus rettgeri	8			1	3	2	2			
Providencia	15		3	1		4	1	1	1	4
Klebsiella pneumoniae	62		14	34	13	1				
Klebsiella ozeae	10		1	5	4					
Enterobacter	45		4	5	4	2	1	4	3	22
Serratia marcescens	37					7	6	5	9	10
Citrobacter freundii	24		2		5		3	2	6	6
Herellea	32			6	16	2				8
Shigella	10	1	4	3	2				1	
Salmonella	24	3	18	3						
Pseudomonas aeruginosa	30									30
Pseudomonas cepacia	10								Ì	10

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single strain from the hospital producing an erroneous picture of either susceptibility or resistance. Some Citrobacter strains were inhibited by concentrations below 25 μ g/ml, but in general Citrobacter strains had high MIC levels like those of Enterobacter cloacae. Sixty-eight per cent of Herellea strains were inhibited by 6.25 μ g/ml. Pseudomonas aeruginosa and Pseudomonas cepacia were resistant to greater than 100 μ g/ml.

Direct comparison of the activity of cefoxitin with the activity of cephalothin and cephloridine is given in Table 3. There was no significant difference in the MIC values against E. coli, P. mirabilis, and Salmonella. However, the activity of cefoxitin against indole-positive Proteae was significant in contrast to the general resistance of these species to cephalothin and cephloridine. The same is true of Serratia, with 45% inhibited by cefoxitin and none by cephalothin or cephloridine.

On the other hand, a better comparison of the activity of cefoxitin against these organisms may be seen in Table 4, which lists the MIC values of carbenicillin, ticarcillin, and ampicillin against *P. morganii*, *P. vulgaris*, and *Enterobacter*. In general, the organisms were more susceptible to the carbenicillin or ticarcillin, but totally resistant to the ampicillin. Isolates tested by the Kirby-Bauer single-disk

technique (1) would be considered resistant to cefoxitin if the susceptibility determination had been on the basis of a cephalothin disk (Table 5). This is particularly true for the indole-positive Proteae, Enterobacter, and Serratia strains. In addition, strains of Herellea, Citrobacter, and a small number of E. coli would be considered resistant to cefoxitin if only cephalothin were the standard of susceptibility to cephalosporin antibiotics, as is the current practice.

The inoculum size was varied from 10^3 to 10^6 CFU. Strains of *E. coli*, *Klebsiella pneumoniae*, *S. marcescens*, *E. cloacae*, *E. aerogenes*, *P. mirabilis*, and *P. morganii* were tested. There was only a two- to fourfold increase in the cefoxitin MIC of susceptible strains when 10^6 CFU was used as compared with use of 10^3 CFU. However, strains with an MIC in excess of 100 μ g/ml were as resistant with an inoculum of 10^3 CFU as with 10^6 CFU.

Use of brain-heart infusion, Trypticase soy, Mueller-Hinton, nutrient, and Columbia media yielded cefoxitin MIC values for E. coli, K. pneumoniae, E. cloacae, P. morganii, P. mirabilis, and S. marcescens which were all within a twofold dilution regardless of the medium used. This is within the error of the method.

Variation of the pH of the medium from 6 to 8 for both gram-positive and gram-negative orga-

Table 3. Comparison of minimal inhibitory concentration of several cephalosporin antibiotics^a

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Organism	Antibiotic	No. of	Percent susceptible at MIC (µg/ml) of:							
	Antibiotic	isolates	1.6	3.12	6.25	10.5	25	50	100	>100
Escherichia coli	Cefoxitin Cephalothin Cephloridine	} 24	4 4	12 ^b 16 20	68 50 92	100 96		100 100		
Klebsiella pneumoniae	Cefoxitin Cephalothin Cephloridine	} 25	4 32 12	12 96 52	88 96	100	100 100			
Proteus mirabilis	Cefoxitin Cephalothin	} 25	8 20	20 28	68 72	72 84	96 88	96		100 100
Proteus, indole positive	Cefoxitin Cephalothin Cephaloridine	} 30			10	26	73	86	100	100 100
Serratia marcescens	Cefoxitin Cephalothin Cephaloridine	} 22				18	30	45	63	100 100 100
Salmonella	Cefoxitin Cephalothin	} 24	84 80	100 100						

^a Values were determined by the agar plate method.

^b Values represent percentage inhibited.

	A	No. of	Percent susceptible at MIC (µg/ml) of:							
Organism	Organism Antibiotic	isolates	1.6	3.12	6.2	12.5	25	50	100	>100
Proteus morganii	Cefoxitin Carbenicillin Ticarcillin Ampicillin	} 16	37 25	62	50	12 75	75 75 100	87 87	100 100	100
Proteus vulgaris	Cefoxitin Carbenicillin Ticarcillin Ampicillin	} 16	50		12 50	62 75	87 100	100		100
Enterobacter	Cefoxitin Carbenicillin Ticarcillin Ampicillin	22	9	9 36 9	18 45	45 54	63 63	81	81	100 100 100

Table 4. Cumulative percentage of isolates susceptible to cefoxitin, carbenicillin, ticarcillin, and ampicillin

Table 5. Susceptibility of gram-negative bacteria to cefoxitin, cephalothin, and carbenicillin^a

Organism	N C	No. of isolates susceptible						
	No. of isolates	Cefox- itin	Cepha- lothin	Carbeni- cillin				
Escherichia coli Klebsiella	36	36	33	29				
pneumoniae	24	20	20	0				
Enterobacter	72	12	4	46				
Serratia	33	8	1	12				
Citrobacter	20	6	5	15				
Herellea	14	11	0	3				
Proteus vulgaris	12	7	0	12				
Proteus			Ŭ					
morganii	6	5	0	6				
Proteus rettgeri	4	4	0	4				
Pseudomonas	25	0	0	21				

^a The Kirby-Bauer method of disk susceptibility was used. Disks contained 30 μ g of cefoxitin, 30 μ g of cephalothin, and 50 μ g of carbenicillin. A zone diameter of 18 mm or greater was used.

nisms revealed no significant effect, and organisms were not rendered susceptible or resistant by alteration of pH of the medium from acid to alkaline.

Resistance to hydrolysis by beta-lactamases. Organisms which were resistant to cephalosporins were selected for study to determine the degree of hydrolysis of cefoxitin by intact bacteria. Table 6 shows the susceptibility of the organisms to ampicillin, cephaloridine, cephalothin, and cefoxitin compared with the amount of antibiotic hydrolyzed. In spite of the resistance of many of these oragnisms to $100 \mu g$ of cefoxitin per ml, only 5 of the 17 strains

hydrolyzed cefoxitin, and the amount hydrolyzed was trivial. E. coli, which possess different types of beta-lactamases according to the Richmond et al. (10) classification, although they hydrolyzed penicillins or cephalosporins efficiently did not appreciably destroy cefoxitin, although two of the strains were resistant to over 200 μ g/ml. Both E. cloacae and E. aerogenes were resistant or susceptible to cefoxitin without regard to the activity of the betalactamase of the intact cell against the antibiotic. The lack of correlation of beta-lactamase activity and resistance to cefoxitin was also seen with Serratia strains, all of which were resistant to cephalothin and one of which was susceptible to ampicillin and cefoxitin. Thus, in these species, E. coli, Enterobacter, Serratia, and *Proteus*, the organisms can be resistant in spite of the stability of cefoxitin to the gram-negative beta-lactamase.

Although intact cells did not hydrolyze cefoxitin, it was possible that strategically placed beta-lactamases could hydrolyze the compound as it entered the cell. For this reason partially purified beta-lactamase preparations were used to determine the resistance of cefoxitin to destruction. Table 7 demonstrates that cefoxitin is also resistant to hydrolysis by different types of beta-lactamase. An E. coli enzyme of the Richmond type III or TEM does not hydrolyze the compound. The activity of this enzyme against penicillins would be at least 100-fold greater. A beta-lactamase from E. cloacae, which is primarily a cephalosporinase even in a purified, isolated state, does not effectively hydrolyze cefoxitin. The induced beta-lactamase from P. aeruginosa, which is primarily a cephalosporinase, also does not destroy cefoxitin. This resist-

Table 6. Susceptibility of organisms to antibiotics in comparison with the amount of antibiotic hydrolyzeda

		Suscep	tibility		Antibiotic hydrolyzed (%)				
Microorganism	Ampi- cillin	Cephlori- dine	Cephalo- thin	Cefox- itin	Ampi- cillin	Cephlori- dine	Cephalo- thin	Cefox- itin	
Escherichia coli 109	R	S	s	S	100	100	10	0	
E. coli 1927	R	R	R	R	100	100	75	0	
E. coli 1929	S	R	R	R	20	85	100	10	
Enterobacter cloacae 670	R	R	R	R	75	75	50	0	
E. cloacae 673	R	R	R	S	0	0	0	0	
E. cloacae 1374	R	R	R	R	70	100	65	5	
Enterobacter aerogenes 1373	S	R	R	S	0	50	25	0	
E. aerogenes 1675	R	R	R	R	10	20	10	0	
Serratia marcescens 1109	R	R	R	R	20	45	50	10	
S. marcescens 1613	S	R	R	S	0	0	5	0	
S. marcescens 1101	R	R	R	R	0	10	10	0	
Proteus mirabilis 1367	R	R	R	R	0	0	0	0	
P. mirabilis 1077	R	R	R	R	100	50	10	0	
P. vulgaris 684	R	R	R	S	100	10	10	0	
P. morganii 1619	R	R	R	R	100	100	100	20	
P. rettgeri 671	R	R	R	R	` 20	20	10	5	
Citrobacter freundii 2017	S	R	R	S	0	72	50	0	

^a S, Susceptible; R, resistant.

Table 7. Hydrolysis of cephalosporin antibiotics by partially purified beta-lactamases

Beta-lactamase	Substrate hydrolyzed (µmol/min)							
	Cefox- itin	Cepha- lothin	Ceph- loridine	Cepha- lexin				
Escherichia coli	< 0.2	4.1	7.0	0.3				
Enterobacter cloacae	0.7	2.6	9.0	7.6				
Proteus morganii	0.2	33.1	7.8	5.6				
Salmonella typhimurium	<0.1	2.3	12.0	0.2				
Pseudomonas aeruginosa	0.2	4.1	18.4	0.7				

ance to hydrolysis is not due to lack of affinity of cefoxitin for beta-lactamases. By using an E. coli TEM beta-lactamase cefoxitin had, with penicillin as substrate, a K_l/K_m of 1×10^{-3} , and with cephaloridine as substrate a K_l/K_m of 1.5×10^{-4} . With the same substrates oxacillin had a K_l/K_m of 2×10^{-4} . This demonstrates that the compound does act as an inhibitor of the hydrolysis of other penicillins and cephalosporins, albeit less efficient than oxacillin.

A possible explanation of the low level of resistance of species such as *Enterobacter* and *Serratia* to cefoxitin, compared with their resistance to other cephalosporin type antibiotics, was investigated by determining the effect of cefoxitin on induction of beta-lactamase. An E. cloacae strain of intermediate susceptibility, cefoxitin MIC of 50 μ g/ml, was exposed to four

Table 8. Effect of previous exposure to cefoxitin and cephalothin

Organism	T	To be the table	Growth (h)a			
	Inducer	Inhibitor	2	3.5	6.5	
Serratia marces-	None	None	28	122	153	
cens 1631	Cephalothin	Cefoxitin	16	23	29	
	Cefoxitin	Cefoxitin	8	78	120	
Proteus morganii	None	None	16	94	153	
1618	Cephalothin	Cefoxitin	0	0	14	
	Cefoxitin	Cefoxitin	33	98	128	
Enterobacter clo-	None	None	22	98	134	
acae 670	Cephalothin	Cefoxitin	23	76	128	
	Cefoxitin	Cefoxitin	21	87	128	

^a Values represent Klett readings. Organisms were grown in the presence of cephalothin (200 μ g/ml) and cefoxitin (25 μ g/ml) to serve as inducing agent. After 3.5 h, a sample from each was removed, washed, and resuspended in medium to which 25 μ g of cefoxitin per ml was added. Organisms were placed in side arm flasks on a water bath shaker at 35 C, and growth was followed with a Klett spectrophotometer.

cephalosporins, namely, cephalothin, cefazolin, cephalexin, and cefoxitin, at a concentration of $25~\mu g/ml$ for 2~h. The organisms were disrupted by sonic treatment, and the beta-lactamase activity was determined. The amount of cephalothin, cephloridine, cephalexin, and cefoxitin hydrolyzed was the same regardless of the inducing cephalosporin. Thus cefoxitin was as effective an inducer of beta-lactamase activity as were cephalothin, cephalexin, and cefazolin.

However, previous exposure to specific cephalosporins does affect the resistance of some

strains. P. morganii and S. marcescens strains which had been grown in the presence of cephalothin were inhibited by cefoxitin (Table 8). But the same strains which had grown in the presence of cefoxitin now grew as well as control organisms. It was not determined whether the strains had increased hydrolytic activity, but other experiments which failed to demonstrate increased beta-lactamase induction would indicate that this was not the explanation. In contrast, an E. cloacae strain which is completely resistant to all cephalosporins was unaffected by previous cefoxitin exposure.

DISCUSSION

Cefoxitin is an analogue of cephamycin C, a family of antibiotics similar to the cephalosporins, but which have been said to exhibit increased resistance to hydrolysis by beta-lactamases of gram-negative organisms (2, 9). This study shows that cefoxitin is less effective than cephalosporin antibiotics such as cephalothin or cephaloridine against gram-positive coccal organisms, but the activity is comparable with that of cephalexin. Cefoxitin activity against E. coli, P. mirabilis, and K. pneumoniae is comparable with the activity of cephalothin, but cefoxitin has activity against an appreciable number of strains of Enterobacter, Citrobacter, indole-positive *Proteae*, and *Herellea*. It should be pointed out, however, that these strains are ones which are susceptible to carbenicillin and ticarcillin. Indeed, as shown in Table 4, most strains of P. morganii and P. vulgaris have a carbenicillin MIC significantly lower than that of cefoxitin. However, use of cephalothin as a standard of cephalosporins would cause a number of cefoxitin-susceptible organisms to be mislabeled as resistant.

Resistance of cefoxitin to hydrolysis by cephalothin-resistant bacteria is easily demonstrated. However, some bacterial strains which failed to hydrolyze cefoxitin were nonetheless resistant. This was true particularly of certain Enterobacter cloacae and Serratia marcescens strains. It is not possible to explain the lack of hydrolysis of cefoxitin by intact bacteria by failure of the cefoxitin to get inside the cell since isolated enzymes did not hydrolyze the antibiotic. Cefoxitin can act as a competitive inhibitor of the hydrolysis of penicillins by beta-lactamases, showing that it does bind to the enzymes. Indeed it might be possible that strategically placed beta-lactamase binds the entering cefoxitin preventing it from reaching its target site in resistant strains. Such a concept could be tested with penicillins which

are good beta-lactamase inhibitors, but inactive against the strains.

The data obtained do not permit one to state conclusively that resistance of cefoxitin to hydrolysis is the important factor in its activity. Preliminary studies in our laboratory with several related compounds suggest that derivatives of this type have a high affinity for receptor sites because these other compounds are highly active, although readily hydrolyzed.

It is not possible from the data presented or from previous investigations (2, 9, 11) to predict whether a particular strain of *Enterobacter*, *Serratia*, or *P. morganii* will be susceptible to cefoxitin. However, strains of these species which are susceptible to carbenicillin or ticarcillin tend to be susceptible to cefoxitin and to another agent, cefamandole (H. C. Neu, manuscript in preparation).

Cefoxitin acts as an inducer of beta-lactamase comparable with other cephalosporin molecules. In one series of experiments, however, the data suggested that prior exposure to cefoxitin caused the organism to become increasingly resistant. Because destruction of antibiotic is not involved, selection of cells with altered cell wall or receptor sites is a possible explanation. Selection of such resistant mutants has occurred in clinical settings with carbenicillin therapy (6).

Extensive animal experiments will have to be conducted to determine the usefulness of cefoxitin in actual infections. The studies of Miller et al. (4) have shown that cefoxitin protects mice against *E. cloacae*. However, further clinical investigation of cefoxitin is clearly indicated.

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