NOTES

IN VITRO ANTIMICROBIAL ACTIVITY COMPARISON OF CEFACLOR (COMPOUND 99638), CEPHRADINE, AND CEPHALOTHIN

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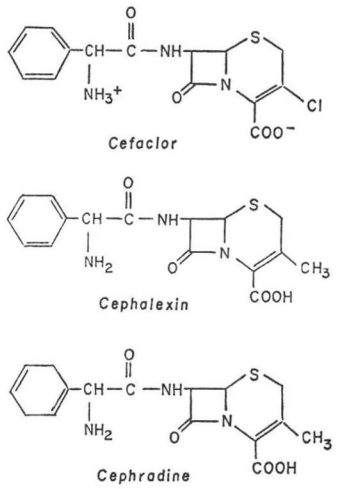
Cefaclor [3-chloro-7-D-(2-phenylglycemamido)-3-cephem-4-carboxylic acid], has been reported by PRESTON and WICK as a new orally absorbed semi-synthetic cephalosporin (14th ICAAC Meeting, paper #426, 1974). This drug is structurally similar to the clinically available oral cephalosporins, cephradine and cephalexin.[4] The significant structural difference is the substitution of a chloro group for the methyl group found in cephalexin and cephradine (Fig. 1).

This study compares the *in vitro* antimicrobial activity of cefaclor with that of cephradine and cephalothin against seven commonly encountered bacterial species.

Organism Sources

One hundred clinical isolates each of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Haemophilus influenzae, Staphylococcus aureus,* and *Streptococcus pyogenes* were studied. *H. influenzae* strains included ten beta-lactamase producing isolates. The haemophilus beta-lactamase was detected by the acidometric penicillinase test[2,7] and confirmed by a chromogenic cephalosporin (Glaxo compound 87/312) method[5]. *S. aureus* isolates tested contained both penicillinase-producing (80%) and deficient (20%) strains. Eighty-three stock serotypes and seventeen untyped clinical isolates of *S. pneumoniae* were also tested. Clinical isolates were consecutive clinical strains from the microbiology laboratories of Kaiser Foundation, St. Francis, and St. Vincent Hospitals. All strains were isolated and identified by standard protocol. Fifteen or more biochemical tests were used for speciation and biotyping of *S. aureus* and the *Enterobacteriaceae* and were performed by the replicator-plate method.[1] Fluorescent antibody method was used to identify *Streptococcus pyogenes.*

Fig. 1. Structural formulae of cefaclor, cephalexin and cephradine



Antibiotic Susceptibility Testing

The antimicrobial activity was assessed by broth microdilution techniques utilizing MUELLER-HINTON (Difco) broth. Organism inoculum concentration was 5×10^5 organisms/ml. For the minimum inhibitory concentration (MIC) determinations of *H. influenzae* and *S. pneumoniae*, 5% supplement C (Difco) and 5% FILDE's reagent, respectively, were added. Incubation was at 35°C for 15~18 hours in a forced air incubator. The MIC was defined as the lowest concentration totally inhibiting bacterial growth (clear well).

Results and Discussion

The cumulative percentage of 100 isolates of *E. coli, Klebsiella pneumoniae, Proteus mirabilis* and *H. influenzae* susceptible to increasing concentrations of cefaclor, cephradine and cephalothin are shown in Table 1. All tested gram-negative species were susceptible to lower cefaclor concentrations than either cephradine or cephalothin. Eighty-two to 100% of these species

groups were inhibited by 4 μg/ml of cefaclor. The differences were very striking with *H. influenzae*, where MIC results were similar to those reported by KAMMER *et al.*[2] The cefaclor mean MIC was 4.5 μg/ml compared to 25.3 μg/ml for cephradine, nearly a six-fold difference. The ten β-lactamase-producing strains had MIC's of 1 μg/ml (1 strain), 2 μg/ml (3 strains), 4 μg/ml (5 strains) and 8 μg/ml (1 strain) and hence were no different than the 90 enzyme-deficient *H. influenzae* isolates. Cefaclor 99638 was similarly more effective than cephalothin (2~4 fold) and cephradine (4~16 fold) against the three *Enterobacteriaceae* species tested.

The gram-positive organism MIC results are shown in Table 2. Generally, cefaclor was slightly more active against *S. aureus*, pneumococcal and Group A streptococcal isolates than cephradine. This was most apparent at the lower concentrations tested. The MICs of both oral antibiotics were consistently less for the streptococci than for *S. aureus*. Cephalothin was more active than either cefaclor or cephradine *versus* the gram-positive strains tested.

The *in vitro* activity of cefaclor appears to be similar to that reported for cefatrizine (BL-S640), another investigational oral cephalosporin.[3,6,8] The slightly wider cefatrizine antimicrobial spectrum, particularly among the *Enterobacteriaceae* has yet to be substantiated for cefaclor.

In conclusion, cefaclor shows an overall *in vitro* antimicrobial activity superior to cephradine. This study tested only those bacterial species for which the oral cephalosporins are currently considered effective. Investigations of a wider variety of organisms are necessary to outline the full antimicrobial spectrum. Also, human clinical pharmacologic and toxicologic studies have yet to be reported for cefaclor.

Summary

Cefaclor showed greater *in vitro* activity than

Table 1. The cumulative percentages of *E. coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Haemophilus influenzae* inhibited by increasing concentrations of cefaclor (CC), cephradine (CD) and cephalothin (CF)

Organism (♯)	Antibiotic	Cumulative % susceptible at MIC (μg/ml) of:					
		≤1	2	4	8	16	32
E. coli (100)	CC	47	64	92	93		96
	CD	1		11	78	94	97
	CF	9	27	63	88	95	96
Klebsiella (100)	CC	94	97	100			
	CD	2	4	11	82	96	97
	CF	32	63	87	95	97	99
P. mirabilis (100)	CC	68	83	90	95	98	100
	CD			1	25	79	95
	CF	22	68	90	97	98	99
H. influenzae (100)	CC	8	24	82	96	100	
	CD	1		10	20	51	79
	CF		7	55	99	100	

Table 2. The cumulative percentages of *Staphylococcus aureus, S. pneumoniae,* and *S. pyogenes* inhibited by increasing concentrations of cefaclor (CC), cephalothin (CF), and cephradine (CD)

Organism (♯)	Antibiotic	Cumulative % susceptible at MIC (μg/ml) of:						
		≤0.125	0.25	0.5	1	2	4	8
S. aureus (100)	CC			1	34	69	90	99
	CD		1	2	18	63	90	98
	CF	39			99			
S. pneumoniae (100)	CC	5	21	98	100			
	CD	8	30	75	100			
	CF	34			100			
S. pyogenes (100)	CC	64	96	98	100			
	CD	46	90	96	98	99	100	
	CF	97			100			

cephradine against all seven bacterial species tested. In addition, cefaclor was more effective than cephalothin *versus E. coli*, *P. mirabilis*, and *Klebsiella*. Gram-positive cephalothin MIC values were consistently lower than either oral cephalosporin.

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