

In Vitro Activity of Cefaclor, a New Orally Administered Cephalosporin Antibiotic

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The in vitro antibacterial activity of cefaclor, cephalothin, and cephalixin against 261 clinical isolates of *Staphylococcus aureus* and *Enterobacteriaceae* was compared. Cefaclor and cephalixin were about equally active against *S. aureus*. Cefaclor was the most active cephalosporin against *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*. The effect on the antimicrobial activity using a relatively high and low inoculum was pronounced for cefaclor when compared with that of cephalothin.

Cefaclor, 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid, is a new oral cephalosporin antibiotic that is structurally related to cephalixin. The present investigation was undertaken to determine the in vitro antibacterial activity of cefaclor compared with that of cephalothin and cephalixin.

MATERIALS AND METHODS

The following strains of bacteria used in this study were isolated from patients at The Medical College of Pennsylvania between July and September 1976: 59 strains of *Staphylococcus aureus*, 53 strains of *Escherichia coli*, 45 strains of *Proteus mirabilis*, 5 strains of indole-positive *Proteus*, 51 strains of *Klebsiella pneumoniae*, and 48 strains of *Enterobacter* species (22 strains of *E. cloacae*, 22 strains of *E. aerogenes*, 2 strains of *E. hafniae*, and 2 strains of *E. agglomerans*).

The susceptibility of the organisms to cefaclor, cephalothin, and cephalixin was determined by an agar-dilution method in Mueller-Hinton agar (MHA) (Difco) and antibiotic medium number 1 (AB1) (Difco). The antibiotics were diluted in two-fold steps in phosphate buffer (pH 4.5). A 1-ml portion of each dilution of antibiotic was added to 9 ml of the respective molten agars to obtain final antibiotic concentrations of 0.098 to 50 µg/ml. The pH of MHA was 7.1 and that of AB1 was 6.6. Bacteria were inoculated onto the surface of the plates by the replicating device of Steers et al. (2). The device delivered approximately 10^6 bacteria to the agar surface (0.001 ml of a 10^{-1} dilution of an overnight culture in heart infusion broth) of each strain to be tested. The minimal inhibitory concentration (MIC) was taken to be the concentration of antibiotic that prevented the visible growth of more than one colony after 24 h of incubation at 37°C. All three antibiotics were tested against a particular bacterial species on the same day.

To study the inoculum effect, 29 strains of *S. aureus*, 27 strains of *E. coli*, and 30 strains of *P. mirabilis* were randomly selected from among the total number of strains originally tested. A 10^{-2}

dilution and an undiluted portion of an overnight culture were inoculated with the replicator onto the surface of plates containing MHA (approximately 10^4 and 10^6 bacteria, respectively). The lower inoculum size approximates that used in the WHO-ICS method and in the study of Bill and Washington (1). The MIC was determined as described above.

The activity of the antibiotics against *S. aureus* in both MHA and AB1 is given in Table 1. Cephalothin was the most active antibiotic against *S. aureus*. Cephalothin was more active in AB1 than in MHA. Cefaclor and cephalixin were about equally active against *S. aureus* in MHA. Both cefaclor and cephalixin were more active in AB1 than in MHA; the activity of cefaclor was enhanced to a much greater extent in AB1 and had activity similar to cephalothin.

Cefaclor was the most active cephalosporin against *E. coli* (Table 1). The activity of cephalothin and cephalixin was similar in MHA and AB1 (Table 1). However, cefaclor was considerably more active in AB1. Cefaclor was as active as cephalothin against *P. mirabilis* and considerably more active than cephalixin (Table 1). Cefaclor was considerably more active in AB1 against *P. mirabilis* than in MHA. Four of five strains of indole-positive *Proteus* were resistant to 50 µg of the three antibiotics per ml. All three antibiotics were inactive against *Enterobacter* species; 43 of 48 strains were resistant to 50 µg of cefaclor or cephalothin per ml, and 38 of 48 strains were resistant to 50 µg of cephalixin per ml. Cefaclor was the most active antibiotic tested against *K. pneumoniae*; cephalothin activity was similar to that of cephalixin (Table 1).

The inoculum effect was considerable for *S. aureus*, *E. coli*, and *P. mirabilis* (Table 2). A total of 34% of *S. aureus* strains, 50% of the *P. mirabilis* strains, and 100% of *E. coli* strains showed greater than or equal to eightfold differences in MIC between high and low inocula with cefaclor. A total of 10% of *S. aureus*, 7% of *P. mirabilis*, and 67% of *E. coli* showed similar differences in MIC between high and low inocula with cephalothin. Percentages for cephalixin were 38, 13, and 59%, respectively. Cefaclor was more active than the other two cephalospo-

TABLE 1. Susceptibility of clinical isolates to cephalosporins^a

Organism (no. of isolates) on:	Cefaclor			Cephalothin			Cephalexin		
	MIC ₅₀	MIC ₇₅	MIC ₉₀	MIC ₅₀	MIC ₇₅	MIC ₉₀	MIC ₅₀	MIC ₇₅	MIC ₉₀
<i>S. aureus</i> (59)									
MHA ^b	3.1	6.3	6.3	0.4	0.4	0.4	6.3	6.3	12.5
AB1 ^c	0.4	0.8	0.8	0.1	0.2	0.4	3.1	3.1	6.3
<i>E. coli</i> (53)									
MHA	12.5	12.5	12.5	25.0	25.0	50.0	12.5	12.5	25.0
AB1	1.6	1.6	3.1	12.5	25.0	50.0	25.0	25.0	25.0
<i>P. mirabilis</i> (45)									
MHA	6.3	12.5	12.5	6.3	12.5	12.5	25	25	50
AB1	1.6	1.6	1.6	3.1	3.1	6.3	12.5	25	25
<i>K. pneumoniae</i> (51)									
MHA	1.6	1.6	12.5	6.3	12.5	>50	6.3	12.5	25
AB1	1.6	3.1	6.3	25	50	>50	25	50	>50

^a Lowest concentration (micrograms per milliliter) of antibiotic inhibiting at least 50, 75, or 90% of strains tested, respectively.

^b Mueller-Hinton agar.

^c Antibiotic Medium 1.

TABLE 2. Comparison of susceptibility of clinical isolates to cephalosporins at high and low inocula^a

Organism (No. of isolates) at inoculum	Cefaclor			Cephalothin			Cephalexin		
	MIC ₅₀	MIC ₇₅	MIC ₉₀	MIC ₅₀	MIC ₇₅	MIC ₉₀	MIC ₅₀	MIC ₇₅	MIC ₉₀
<i>S. aureus</i> (29)									
High	6.3	12.5	12.5	0.8	0.8	1.6	6.3	12.5	12.5
Low	0.8	1.6	1.6	0.2	0.2	0.4	1.6	3.1	3.1
<i>E. coli</i> (27)									
High	25	25	>50	>50	>50	>50	50	50	>50
Low	0.8	1.6	3.1	6.3	12.5	25	6.3	6.3	6.3
<i>P. mirabilis</i> (30)									
High	6.3	12.5	25.0	12.5	12.5	12.5	50	50	50
Low	1.6	1.6	1.6	6.3	6.3	6.3	12.5	12.5	12.5

^a Lowest concentration (micrograms per milliliter) of antibiotic inhibiting at least 50, 75, or 90% of strains tested, respectively.

rins even against a high inoculum size of *E. coli* and *P. mirabilis*.

In both MHA and AB1, cefaclor was the most active of the three cephalosporins tested against *Enterobacteriaceae*, inhibiting 45% of *E. coli*, 71% of *P. mirabilis*, and 83% of *K. pneumoniae* at 6.3 µg/ml. Compared with cephalexin, cefaclor was especially active against *P. mirabilis*. Our study confirms the increased activity of cefaclor compared with cephalexin against *Enterobacteriaceae* recently reported by Bill and Washington (1). However, our study differs from the latter in that cefaclor appeared to be much more active against *P. mirabilis*. Preliminary unpublished data indicate that peak serum levels after a 500-mg dose of cefaclor should readily exceed 6.3 µg/ml, and urine levels should be much higher. Cefaclor's greater activity in AB1 than in MHA may be due to the more acid pH of AB1 and greater stability of cefaclor at lower pH (a po-

tential advantage in the treatment of many urinary tract infections) but may be also due to other differences between the two media. The inoculum effect was pronounced for cefaclor when compared with that of cephalothin.

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