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NOTES

Activity of Cefamandole and Other Cephalosporins Against Aerobic and Anaerobic Bacteria

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The activity of cefamandole was comparable to that of cephalothin, cefazolin, and cephaloridine against *Staphylococcus aureus, Streptococcus pyogenes,* and *Diplococcus pneumoniae*. In contrast, cefamandole was considerably more active than cephalothin, cefazolin, or cephaloridine against gram-negative facultative bacilli, including *Haemophilus influenzae,* the most striking disparities being noted with indole-positive *Proteus* and *Enterobacter*. *Bacteroides fragilis* was more susceptible to cefoxitin than to cefamandole or cefazolin (median minimal inhibitory concentration, approximately 8, 32, and 32 μg/ml, respectively); cephalothin exhibited still less activity against this species. The majority of other anaerobes were inhibited by relatively low concentrations of all four cephalosporins. The results indicate a potentially valuable role for cefamandole against facultative gram-negative bacilli, including *H. influenzae,* but no exceptional activity against anaerobes.

Two new cephalosporins currently under investigation appear to offer some unique features that may broaden the therapeutic usefulness of this class of drugs. Cefamandole is a recently described derivative of 7-aminocephalosporanic acid which exhibits striking activity against a variety of facultative gram-negative bacilli (2, 4, 5, 8) including *Haemophilus influenzae* (3, 9). This broader spectrum correlates to some extent with its relative resistance to hydrolysis by various beta-lactamases (5, 8). Cefoxitin, a member of the cephamycin group of cephalosporins, also displays increased resistance to various beta-lactamases; this investigational drug shows exceptional activity against *Bacteroides fragilis* as well as many facultative gram-negative bacilli (7).

The purpose of the present study was to compare the in vitro activity of cefamandole with that of cephalothin, cefazolin, and cephaloridine against a variety of aerobic and facultative bacteria, and with cefoxitin against anaerobic isolates.

Antibiotics. The lithium salts of cefamandole, sodium cephalothin, sodium cefazolin, and cephaloridine were supplied as dry sterile powders by Eli Lilly & Co., Indianapolis, Ind.; cefoxitin was provided by Merck Institute (Rahway, N. J.).

Bacterial strains. Aerobic and facultative aerobic isolates were obtained from the clinical laboratories of Tufts-New England Medical Center Hospital, Boston, Mass. These were generally lyophilized and reconstituted shortly before use. The strains of *Salmonella,* which included *S. typhosa, S. typhimurium,* and *S. enteritidis,* were provided through the courtesy of the State Laboratory Institute, Massachusetts Department of Public Health, Jamaica Plain, Mass. The sources and characterization of the anaerobic bacteria have been described (7). One strain of *B. clostridiiformis* highly resistant to penicillin G was kindly supplied by Victor E. Del Bene, Medical University of South Carolina, Charleston.

Procedures. Antibiotic susceptibility of aerobes was measured by a twofold broth microdilution technique (1) using Trypticase soy broth (Difco) as diluent for most organisms. Todd-Hewitt broth (Difco), enriched with 0.5% human serum, and Trypticase soy broth with 5% Fildes supplement (Oxoid) were used for

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studies of *Diplococcus pneumoniae* and *H. influenzae*, respectively. Bacterial inocula, prepared from an overnight broth culture, contained 5×10^3 organisms per well. The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) were determined as previously described (1).

A modified agar dilution method utilizing chamber techniques was used to determine susceptibility of anaerobes (7).

Aerobic and facultative organisms. Staphylococci, streptococci, and *D. pneumoniae* were highly susceptible to the four cephalosporins examined, with cephaloridine exhibiting slightly greater activity than the other congeners (Table 1). Enterococci were relatively insusceptible to cephalothin, cefazolin, and cefamandole but were inhibited by 16 μg of cephaloridine per ml.

Cefamandole was considerably more active than the other cephalosporins against gram-negative facultative organisms (Table 2). Almost all strains were inhibited by 4 μg of cefamandole per ml, and none required more than 16 μg/ml. The activity of this cephalosporin was generally four- to eightfold greater than that of the other compounds against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella,* and *H. influenzae*. Even more striking disparities were evident with indole-positive strains of *Proteus* and with *Enterobacter*. These were inhibited by cefamandole in concentrations of 16 and 4 μg/ml, respectively, but were usually resistant to 64 μg of the other agents per ml. The MIC of all four cephalosporins for five strains of *Pseudomonas aeruginosa* exceeded 128 μg/ml.

The MBC was generally within one dilution of the MIC for all aerobic and facultative organisms studied.

Anaerobic organism. Cefoxitin was studied in place of cephaloridine because of its striking activity against *B. fragilis* (7) (Table 3). This characteristic was evident in the present study; over half of the strains were inhibited by 8 μg/ml, and virtually all were inhibited by 32 μg of cefoxitin per ml. Cefamandole and cefazolin were about one-quarter as active as cefoxitin against *B. fragilis*, half the isolates requiring at least 32 μg/ml for inhibition. Cephalothin was the least active agent against this species.

Clostridia were inhibited by each of the cephalosporins at concentrations ≤8 μg/ml, with no striking differences among the compounds. The same was true of the anaerobic cocci; one organism in this group, however, a *Streptococcus intermedius*, was relatively resistant to cefoxitin. Among the organisms grouped as "others," the large majority was inhibited by all four drugs in concentrations ≤4 μg/ml; the more resistant strains consisted of the penicillin-resistant isolate of *B. clostridiiformis* and two *Eubacterium lentum*.

The data for aerobic and facultative organisms in the present study are in reasonably close agreement with those of other authors (1-5, 7-9). The gram-positive cocci examined were, with the exception of the enterococcus, readily inhibited by all four cephalosporins; enterococci were relatively resistant but appeared to be somewhat more susceptible to cephaloridine than to the other congeners (1, 2). In contrast, the activity of these cephalosporins against fa-

TABLE 1. *Activity of cephaloridine, cefazolin, cephalothin, and cefamandole against facultative gram-positive bacteria*

Species (no. of strains)	Antibiotic	Cumulative % susceptible at MIC (μg/ml) of:											
		<0.03	0.03	0.06	0.125	0.25	0.50	1.0	2.0	4.0	8.0	16.0	32.0	64.0
Staphylococcus aureus (10)	Cephaloridine	50	50	90	100									
	Cefazolin			90	100									
	Cephalothin				50	100								
	Cefamandole			10	40	50	100							
S. pyogenes (8)	Cephaloridine	38	38	38	100									
	Cefazolin		100											
	Cephalothin				100									
	Cefamandole	63	63	63	100									
D. pneumoniae (10)	Cephaloridine					70	100							
	Cefazolin					20	60	100						
	Cephalothin					10	90	100						
	Cefamandole					20	60	90	100					
Enterococcus (10)	Cephaloridine								10	20	50	100		
	Cefazolin												30	90
	Cephalothin												20	90
	Cefamandole												20	100

TABLE 2. *Activity of cephaloridine, cefazolin, cephalothin, and cefamandole against facultative gram-negative bacilli*

Species (no. of strains)	Antibiotic	Cumulative % susceptible at MIC (μg/ml) of:										
		0.06	0.125	0.25	0.50	1.0	2.0	4.0	8.0	16.0	32.0	64.0
E. coli (9)	Cephaloridine						11	44	77	100		
	Cefazolin				11	55	88	88	88	88	88	100
	Cephalothin								11	88	88	88
	Cefamandole					22	66	100				
K. pneumoniae (10)	Cephaloridine						20	60	90	90	90	100
	Cefazolin				10	20	50	60	90	100		
	Cephalothin					10	10	30	60	90	100	
	Cefamandole				30	60	60	90	100			
P. mirabilis (10)	Cephaloridine							50	90	100		
	Cefazolin						10	40	80	100		
	Cephalothin					10	30	70	80	100		
	Cefamandole		10	20	40	90	90	100				
Indole-positive *Proteus* (8)	Cephaloridine					13	13	13	13	13	13	13
	Cefazolin			13	13	13	13	13	13	13	13	13
	Cephalothin			13	13	13	13	13	13	13	13	13
	Cefamandole		13	40	65	78	78	78	78	100		
Enterobacter (9)	Cephaloridine				22	22	22	22	33	33	33	44
	Cefazolin						11	11	11	11	11	33
	Cephalothin									11	11	11
	Cefamandole				22	44	66	100				
Salmonella (8)	Cephaloridine		13	13	25	75	100					
	Cefazolin			13	50	100						
	Cephalothin				13	38	88	88	100			
	Cefamandole		38	75	100							
H. influenzae (10)	Cephaloridine	10	10	20	40	60	100					
	Cefazolin	10	10	10	10	10	20	40	90	100		
	Cephalothin	30	40	50	80	100						
	Cefamandole	70	80	90	100							

TABLE 3. *Activity of cefoxitin, cefazolin, cephalothin, and cefamandole against anaerobic bacteria*

Species (no. of strains)	Antibiotic	Cumulative % susceptible at MIC (μg/ml) of:										
		0.125	0.25	0.50	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128	256
B. fragilis (53)	Cefoxitin			4		6	34	62	90	98	100		
	Cefazolin				2		6	8	15	57	85	87	98
	Cephalothin			4						19	40	81	85
	Cefamandole				2		4		23	57	87	89	100
Clostridium[a] (21)	Cefoxitin	5		33	48	81	95	100					
	Cefazolin	24		48	71	90	100						
	Cephalothin			10	43	57	86	100					
	Cefamandole	10		19	38	76	90	100					
Anaerobic cocci[b] (16)	Cefoxitin	13		25	50	63	88	94		100			
	Cefazolin	13		45	56	69	94	100					
	Cephalothin	19		37	50	88	94	100					
	Cefamandole	13		25	50	63	69	81	100				
Others (20)[c]	Cephoxitin	30		55		60	85			100			
	Cefazolin	55		75	95						100		
	Cephalothin	60		65	70	95						100	
	Cefamandole	40		75	85	90	95				100		

[a] Includes *C. perfringens* (13 strains), *C. bifermentans* (5), *C. paraputrificum* (3), and *C. barati* (1).
[b] Includes peptostreptococci (5 strains), peptococci (3), anaerobic cocci (5), and *S. intermedius* (3).
[c] Includes *Veillonella* (3 strains), *Acidaminococcus* (1), *Fusobacterium* (2), *Bacteroides* spp. (5), *Eubacterium* (4), and *Propionibacterium* (5).

cultative gram-negative bacilli showed marked disparities, with cefamandole being considerably more inhibitory than the other agents. This was especially noteworthy with indole-positive *Proteus* and *Enterobacter* species, an observation in accord with previously published data (2, 5). Cefamandole showed striking activity against *H. influenzae,* as has been reported elsewhere (2–4, 9). Although we did not study this, others have found a minimal (8) or inconsistent (5) effect of different media on the activity of cefamandole. Similarly, an important influence of inoculum size has been detected by some authors (2, 4) but not by others (8). Neu described a variable effect of inoculum size, most marked with intrinsically resistant bacilli that did not produce high levels of beta-lactamase (5). Except for Eykyn et al. (2), most authors found, as we did, that the MBC of cefamandole was within one or two dilutions of the MIC (4, 5, 8).

The four cephalosporins studied showed similar and pronounced activity against most anaerobes, except for *B. fragilis*. These data for cefoxitin, cefazolin, and cephalothin are in general agreement with those reported previously (6, 7). *B. fragilis* was much more susceptible to cefoxitin than to the other agents, with 90% of strains inhibited by 16 μg or less per ml. The activity of cefamandole was almost identical to that of cefazolin (median MIC, 32 μg/ml), whereas cephalothin was the least potent agent studied.

The results of these studies indicate that cefamandole is more active than commercially available cephalosporins against a variety of facultative gram-negative bacilli, especially indole-positive *Proteus* and *Enterobacter* species; moreover, the drug is highly inhibitory to *H. influenzae,* a property that may be of clinical usefulness. The anaerobic spectrum of cefamandole is similar to that of cefazolin, and both agents display less activity than does cefoxitin against *B. fragilis*.

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