ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1976, p. 1066-1069

Vol. 9, No. 6
Printed in U.S.A.

NOTES

Comparison of In Vitro Antimicrobial Activity of Cefamandole and Cefazolin with Cephalothin Against over 8,000 Clinical Bacterial Isolates

RONALD N. JONES* AND PETER C. FUCHS

Department of Pathology, Kaiser Foundation Hospital Laboratories, Portland, Oregon 97217, and Department of Pathology, St. Vincent Hospital and Medical Center, Portland, Oregon 97225*

Received for publication 8 January 1976

Antimicrobial susceptibility to cefamandole versus cephalothin and cefazolin versus cephalothin was compared by the broth microdilution method against 3,000 and 5,895 clinical bacterial isolates, respectively. Cefamandole and, to a lesser degree, cefazolin showed greater activity than cephalothin against *Enterobacteriaceae*, but the three drugs were comparable against gram-positive cocci.

The currently available 3-heterocyclic-thiomethyl cephalosporin, cefazolin, enjoys wide clinical usage because of its many desirable pharmacological properties, such as: (i) sustained high concentrations in serum and tissue, (ii) low toxicity at therapeutic concentrations, (iii) relative lack of pain on intramuscular injection, and (iv) wide antimicrobial spectrum. An early publication in Japan (8) and later ones in the United States (1, 4, 5, 7-11) have documented greater antimicrobial activity of cefazolin than of cephalothin against the *Enterobacteriaceae*.

Cefamandole, another 3-heterocyclic-thiomethyl cephalosporin, is not yet available for clinical use, but early studies have also suggested that it has greater in vitro antimicrobial activity than cephalothin (2, 6, 12).

The present study compares the in vitro antimicrobial activity of cefamandole and cephalothin against 3,000 clinical bacterial isolates as well as the activity of cefazolin and cephalothin against 5,895 different clinical isolates.

The organisms studied were consecutive routine clinical bacterial isolates from the clinical microbiology divisions of Kaiser Foundation Laboratories, Oregon region. Approximately half of all isolates tested were urinary pathogens. Eighty-seven percent of all isolates were gram-negative bacilli. Bacteria were identified by the replicator method described by Fuchs (3). Additional tests and procedures were utilized when indicated.

Cefazolin was furnished by Eli Lilly & Co. and by Smith, Kline and French Co. Cephalothin laboratory standard and cefamandole lithium were supplied by Eli Lilly Research Laboratories.

Minimal inhibitory concentrations (MIC) were determined by a broth microdilution method. Mueller-Hinton broth (Difco) containing seven serial twofold dilutions of the appropriate antimicrobial were placed in microdilution wells in volumes of 0.1 ml. The antimicrobial dilution schedule ranged from 1 to 64 μg/ml for the cefamandole comparison and 1.25 to 80 μg/ml for the cefazolin comparison. Inocula were prepared and diluted so that, after final delivery to the wells (by the automated inoculators of either Micro-Media Systems, Inc. or Canalco-Ames), the concentration was 1.5×10^5 colony-forming units per ml.

Bactericidal activity was tested for all three drugs against 10 to 25 isolates of each of the seven commonly encountered species. The minimal bactericidal concentrations (MBC) were determined by subculturing 1 μl from each well of an MIC tray to a tray containing Mueller-Hinton broth without antimicrobials. The lowest concentration yielding no growth at 24 h was considered the MBC—a greater than 99% kill end point.

The results of in vitro antimicrobial activity against gram-negative bacteria are recorded for cefamandole and cephalothin in Table 1 and for cefazolin and cephalothin in Table 2. Against the *Enterobacteriaceae* both cefamandole and cefazolin showed greater activity than cephalothin at the usual therapeutic concentrations.

The only exception to this generalization was the slightly greater resistance of *Proteus mirabilis* to cefazolin compared with cephalothin.

TABLE 1. *In vitro susceptibility of 2,217 gram-negative bacillus isolates to cefamandole (CM) and cephalothin (CF)*

Organism	No. of isolates	Antimicrobial	Cumulative % susceptible at MIC (μg/ml) of:							
			1	2	4	8	16	32	64	>64
E. coli	1,595	CM	87	94	97	98	99			100
		CF	7	17	50	83	94	97		100
K. pneumoniae	203	CM	78	90	97	98				100
		CF	14	51	84	95	97			100
Enterobacter cloacae	40	CM	23	40	58	68	75	78	90	100
		CF					3	10	18	100
E. aerogenes	9	CM	55	77		88		100		
		CF				11	22	55	77	100
Serratia marcescens	7	CM	14			29	87	100		
		CF								100
Citrobacter freundii	29	CM	86	90					97	100
		CF					11	50	61	100
P. mirabilis	147	CM	89	95	99	100				
		CF	16	60	86	97	100			
P. morganii	23	CM	65	74		83	87		96	100
		CF						9	22	100
P. rettgeri	11	CM	54	72	90	100				
		CF	9				18		27	100
P. vulgaris	11	CM	18	27	45	63		72	81	100
		CF							9	100
Miscellaneous *Enterobacteriaceae*	11[a]	CM	73	82	91				100	
		CF	27	45	64	73				100
P. aeruginosa	87	CM							1	100
		CF								100
Acinetobacter anitratus	21	CM			5		10	50	84	100
		CF								100
Pasteurella multocida	7	CM	100							
		CF	100							
Miscellaneous non-*Enterobacteriaceae*	16[b]	CM	50	56	69		81	94	100	
		CF	38			44		56	75	100

[a] Includes five *C. diversus*, three *E. agglomerans*, and three *Providencia stuartii* isolates.
[b] Includes five *A. lwoffi*, five *Aeromonas hydrophilia* isolates, and single isolates of six other species.

Although two separate populations of organisms were tested, cefamandole appears to exhibit greater activity than cefazolin.

Among non-*Enterobacteriaceae* gram-negative bacilli, *Pseudomonas aeruginosa* was uniformly resistant to all three drugs. Among the other microbes of this group, the susceptibility patterns were variable, but in general cefamandole and cefazolin showed greater activity than cephalothin.

Gram-positive cocci, with the exception of enterococci, were quite susceptible to the three drugs, the majority being inhibited by the lowest concentration tested. The enterococci, 95% of which were *Streptococcus faecalis*, were generally resistant. No consistent or significant differences in susceptibility between the three antimicrobials was noted with the gram-positive cocci.

Comparison of MIC and MBC end points for each of the three drugs against *Escherichia coli, Klebsiella pneumoniae, P. mirabilis*, indole-positive *Proteus, S. faecalis*, and group B streptococci showed no significant differences, indicating the inhibitory activity of these cephalosporins is bactericidal.

This study of a large number of clinical isolates confirms cefazolin is more active in vitro

TABLE 2. *In vitro susceptibility of 5,559 gram-negative bacillus isolates to cefazolin (CZ) and cephalothin (CF)*

Organism	No. of isolates	Antimicrobial	Cumulative % susceptible at MIC (μg/ml) of:							
			1.25	2.5	5	10	20	40	80	>80
E. coli	2,992	CZ	76	87	93	97	98		99	100
		CF	11	36	76	92	96		97	100
K. pneumoniae	614	CZ	67	83	93	96	97	98	99	100
		CF	49	76	89	95	97	99		100
E. cloacae	225	CZ	21	43	50	54	60	70	80	100
		CF	1	2	3	8	9	14	22	100
E. aerogenes	112	CZ	16	46	62	73	82	91	98	100
		CF	3	7	10	21	46	69	79	100
E. agglomerans	62	CZ	65	79	87	89	90	92	95	100
		CF	38	48	62	69	80	82	87	100
S. marcescens	46	CZ	6	10	15	20		25	39	100
		CF								100
C. freundii	92	CZ	26	53	73	80	88	95		100
		CF	3	5	15	52	80	87	95	100
C. diversus	57	CZ	67	86	98	100				
		CF	40	61	69	88	95	98	99	100
P. mirabilis	361	CZ	12	67	87	94	98	99		100
		CF	29	76	93	97	98			100
P. morganii	49	CZ	2	9	16	18		23	39	100
		CF							2	100
P. rettgeri	16	CZ	50	68	81	88	100			
		CF	13	19		25	56	75	88	100
P. vulgaris	10	CZ						30	50	100
		CF							10	100
Miscellaneous *Enterobacteriaceae*	70[a]	CZ	49	74	84	92	96	100		
		CF	26	46	56	67	77	79		100
P. aeruginosa	494	CZ								100
		CF								100
A. anitratus	168	CZ	18	23	24	26	28	35	51	100
		CF				1	2	4	14	100
Miscellaneous non-*Enterobacteriaceae*	191[b]	CZ	27	34	40	46	56	63	74	100
		CF	24	28	29	37	44	47	51	100

[a] Includes 30 *Salmonella enteritidis*, 13 *Shigella sonnei*, 8 *P. stuartii*, 5 *S. liquefaciens*, 5 *Alkalescens-Dispar*, 3 *E. hafniae*, 3 enteropathogenic *E. coli*, 2 *S. flexneri*, and 1 *S. dysenteriae* isolate.

[b] Includes 40 *A. lwoffi*, 29 *Moraxella* sp., 29 *P. maltophilia*, 13 *P. fluorescens*, 12 *A. hydrophilia*, 12 *P. multocida*, and 15 species with less than 10 isolates each.

than cephalothin against gram-negative organisms (1, 4, 5, 7–11) and confirms also the greater cefamandole activity (2, 6, 12). This increased activity of cefamandole coupled with its relatively low protein binding (compared with cefazolin) should encourage in vivo investigation of its usefulness.

LITERATURE CITED

1. **Bergeron, M. G., J. L. Brusch, M. Barza, and L. Weinstein.** 1973. Bactericidal activity and pharmacology of cefazolins. Antimicrob. Agents Chemother. 4:396–401.
2. **Eykyn, S., C. Jenkins, A. King, and I. Philips.** 1973. Antibacterial activity of cefamandole, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin, and cephalexin. Antimicrob. Agents Chemother. 3:657–661.
3. **Fuchs, P. C.** 1975. The replicator method for identification and biotyping of common bacterial isolates. Lab. Med. 6 (5):6–11.
4. **Kirby, W. H. M., and C. Regamey.** 1973. Pharmacokinetics of cefazolin compared with four other cephalosporins. J. Infect. Dis. 128(Suppl):S341–S346.

5. **Motley, M., and S. Shadomy.** 1974. In vitro studies with cefazolin. Antimicrob. Agents Chemother. 6:856–861.
6. **Neu, H. C.** 1974. Cefamondole, a cephalosporin antibiotic with an unusually wide spectrum of activity. Antimicrob. Agents Chemother. 6:177–182.
7. **Nishida, M., T. Matsubara, T. Marakawa, Y. Mine, Y. Yokota, S. Kuwahara, and S. Goto.** 1970. In vitro and in vivo evaluation of cefazolin, a new cephalosporin C derivative, p. 236–243. Antimicrob. Agents Chemother. 1969.
8. **Phair, J. P., J. Carleton, and J. S. Tan.** 1972. Comparison of cefazolin, a new cephaolsporin antibiotic, with cephalothins. Antimicrob. Agents Chemother. 2:329–330.
9. **Reller, L. B., W. W. Karney, H. N. Beaty, K. K. Holmes, and M. Turck.** 1973. Evaluation of cefazolin, a new cephalosporin antibiotic. Antimicrob. Agents Chemother. 3:483–497.
10. **Ries, K., M. E. Levison, and D. Kaye.** 1973. Clinical and in vitro evaluation of cefazolin, a new cephalosporin antibiotic. Antimicrob. Agents Chemother. 3:168–174.
11. **Sabath, L. D., C. Wilcox, C. Garner, and M. Finland.** 1973. In vitro activity of cefazolin against recent clinical bacterial isolates. J. Infect. Dis. 128(Suppl):S320–S326.
12. **Wick, W. E., and D. A. Preston.** 1972. Biological properties of three 3-heterocyclic-thiomethyl cephalosporin antibiotics. Antimicrob. Agents Chemother. 1:221–234.