ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1977, p. 47-50

Vol. 12, No. 1
Printed in U.S.A.

Cefuroxime, a New Parenteral Cephalosporin: Collaborative In Vitro Susceptibility Comparison with Cephalothin Against 5,887 Clinical Bacterial Isolates

RONALD N. JONES,* PETER C. FUCHS, THOMAS L. GAVAN, E. HUGH GERLACH, A. L. BARRY, AND CLYDE THORNSBERRY

Department of Pathology, Kaiser Foundation Hospital Laboratories, Portland, Oregon 97217; Department of Pathology, St. Vincent Hospital, Portland, Oregon 97225; Department of Microbiology, Cleveland Clinic Foundation, Cleveland, Ohio 44106; Microbiology Laboratory, St. Francis Hospital, Wichita, Kansas 67201; Clinical Microbiology Laboratory, University of California (Davis), Sacramento Medical Center, Sacramento, California 95817; Antimicrobic Investigation Section, Center for Disease Control, Atlanta, Georgia 30333*

Received for publication 4 March 1977

Cefuroxime, a new parenteral cephalosporin was compared with cephalothin by broth microdilution susceptibility testing against 5,887 routine clinical bacterial isolates in four large clinical laboratories. The minimal inhibitory concentrations (MICs) of cefuroxime against the *Enterobacteriaceae* were consistently lower than those of cephalothin. This was most striking among the *Enterobacter* species, which were generally susceptible to cefuroxime (MIC $\leq$ 8 μg/ml), but resistant to cephalothin. Similar results occurred with *Haemophilus* species, *Acinetobacter anitratus*, meningococci, and *Aeromonas hydrophilia*, but *Pseudomonas* species and enterococci were resistant to high concentrations of both drugs. Streptococci showed slightly greater susceptibility to cefuroxime than to cephalothin. By contrast, staphylococci were more susceptible to cephalothin. *Bacteroides fragilis* was resistant to cefuroxime, but other anaerobes were generally susceptible.

Cefuroxime [(6R,7R)-3-carbamoyloxymethyl-7-(2Z)-2-methoximino(fur-2-yl)-acetamidoceph-3-em-4-carboxylic acid] is a new semisynthetic cephalosporin. This parenteral antibiotic has a broad antimicrobial spectrum offering potential therapeutic advantages over currently available cephalosporins (2, 3, 6-10).

This study compares its in vitro antimicrobial activity with that of cephalothin. The study uses a large number of clinical bacterial isolates from four collaborating laboratories in three widely separated geographic areas.

MATERIALS AND METHODS

Antibiotics. Cefuroxime sodium was obtained from Glaxo Research Ltd., Greenford, Middlesex, England. Cephalothin laboratory-standard powder was provided by Eli Lilly Research Laboratories, Indianapolis, Ind.

Bacterial isolates. The organisms used in this study were consecutive clinical strains isolated in the clinical microbiology laboratories of the Cleveland Clinic (Cleveland, Ohio); Kaiser Foundation Hospitals (Portland, Oreg.); St. Francis Hospital (Wichita, Kans.); and St. Vincent Hospital (Portland, Oreg.). A total of 5,803 aerobic and facultative anaerobic strains were tested plus an additional 84 strict anaerobes. Each isolate was processed and identified by a standard procedure of 10 to 24 biochemical tests. Identification was performed by the replicator-plate method described by Fuchs (4) or by the API system. Additional phage typing, serological typing, fluorescent antibody identification, countercurrent immunoelectrophoresis procedures, and antimicrobial agent susceptibility patterns were used where needed.

Antimicrobial susceptibility testing. Minimum inhibitory concentrations (MIC) for all antimicrobial agents were determined by the microdilution broth technique. Mueller-Hinton broth (Difco) was commercially dispensed in plastic trays (Micro Media Systems, Campbell, Calif.) or in an MIC-2000 (Cooke Laboratory Products, Alexandria, Va.) from collaborating laboratories. The antimicrobial agents were dispensed in the tray wells in 100-μl volumes. A total of seven twofold (cefuroxime and cephalothin) dilutions were utilized. Automatic inoculators were used to dispense 1 to 5 μl to each 100-μl well. Inoculum size was adjusted to achieve a final concentration of 5×10^5 organisms per ml. Quality control of the inoculum size concentration was performed by pour-plate and quantitative loop techniques.

MIC end points were defined as the lowest well concentration totally inhibiting organism growth (clear well), after 15 to 18 h of incubation at 35°C in a forced-air incubator.

Quality-control strains of known MIC values were run daily parallel with the unknown strains. These quality-control strains included *Escherichia*

coli (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), and *Streptococcus faecalis* (ATCC 29212). A total of 658 MIC quality-control end point determinations were made during the study interval. Only five (0.73%) MIC values were outside the acceptable ±1 dilution limits at the four collaborating laboratories.

Susceptibility testing of *S. pneumoniae*, several beta-hemolytic streptococci, and *Haemophilus* species was performed in Mueller-Hinton broth supplemented with 5% peptic digest of horse cells. For anaerobic susceptibility testing, brain heart infusion broth containing 0.1 μg of menadione and 0.01 μg of hemin per ml and the methods described previously (5) were used.

RESULTS

Comparisons of cefuroxime and cephalothin MICs against the *Enterobacteriaceae* are shown in Table 1. Generally, cefuroxime appeared to be a more effective agent than cephalothin for each of the *Enterobacteriaceae* species. Of the *Enterobacter* species tested, 311 of 357 were inhibited by concentrations of 32 μg/ml or less. *Serratia marcescens* demonstrated a limited susceptibility to cefuroxime with 57% of strains inhibited by 32 μg/ml. By contrast, all six isolates of *S. liquefaciens* (*E. liquefaciens*) were inhibited by a concentration of 8 μg/ml. Cephalothin showed minimal activity against both *Serratia* species. Forty-seven strains of *Proteus morganii* were tested and found to be more susceptible to cefuroxime than to cephalothin. Of these isolates, 83% were inhibited at 32 μg of cefuroxime per ml or less as compared with 13% at this concentration of cephalothin. *P. rettgeri* was even more susceptible to cefuroxime with two-thirds of the isolates susceptible at 8 μg/ml compared with 18% for cephalothin. *P. vulgaris* was the least susceptible of the indole-positive *Proteus* group, with only one-third of the isolates susceptible at tested concentrations. More *Citrobacter diversus* strains were susceptible to 2 μg of cephalothin (37%) per ml than to this concentration of cefuroxime (9%). At higher concentrations, no appreciable difference was noted.

Table 2 shows the comparative susceptibility to cefuroxime and cephalothin commonly encountered in non-*Enterobacteriaceae* gram-negative organisms. The characteristic resistance of *P. aeruginosa* and other *Pseudomonas* species to cephalosporin compounds was generally true for cefuroxime. Eighty percent of the strains of *Acinetobacter calcoaceticus* subspecies *anitratus* (Herellea) were inhibited at 32 μg or less of cefuroxime per ml. *H. influenzae* and *Haemophilus* species were consistently inhibited at lower concentrations of cefuroxime as compared with those of cephalothin.

Table 3 compares cefuroxime and cephalothin against 1,334 clinical isolates of gram-positive cocci plus 25 strains of *Neisseria meningitidis*. Cephalothin was consistently more active than cefuroxime against staphylococcal isolates. For the *Streptococcus* species tested, cefuroxime appeared to be slightly more active

TABLE 1. *Cefuroxime and cephalothin susceptibility comparisons against 3,691 clinical isolates of Enterobacteriaceae*

Organism (no.)	MIC (cefuroxime/cephalothin)[a] required for given % of isolates		
	25	50	90
Escherichia coli (1,940)	1.3/2.6	1.9/4.0	5.0/13.0
Klebsiella pneumoniae (582)	0.8/1.7	1.4/2.7	3.5/6.6
Enterobacter cloacae (169)	2.7/32	5.2/>32	>32/>32
E. aerogenes (137)	1.2/10.8	1.9/19	8.0/>32
E. agglomerans (41)	1.3/4.8	2.6/14.0	32/>32
Serratia marcescens (100)	13/>32	25/>32	>32/>32
Proteus mirabilis (442)	<0.5/1.6	0.6/2.1	1.3/4.6
P. morganii (47)	6.0/>32	11.0/>32	>32/>32
P. rettgeri (16)	<0.5/18.0	0.9/>32	>32/>32
P. vulgaris (21)	9.0/>32	>32/>32	>32/>32
Providencia species (18)	0.8/20	1.1/>32	>32/>32
Citrobacter diversus (46)	2.5/2.0	3.2/2.4	8.0/8.0
C. freundii (56)	1.2/8.0	1.7/16.0	8.0/>32
Salmonella species (10)	1.1/1.1	2.1/1.5	3.2/2.8
Shigella species (21)	1.1/2.6	1.8/3.9	3.3/16.0
Others[b] (45)	0.7/2.3	1.4/7.4	5.0/>32

[a] MIC values (micrograms per milliliter) derived from log-probit plots.

[b] Includes *K. ozaenae* (18), *K. rhinoscleromatis* (2), *S. liquefaciens* (6), enteropathogenic *E. coli* (10), *Edwardsiella tarda* (4), *Enterobacter hafniae* (4), and *Yersinia enterocolitica* (1).

TABLE 2. *Susceptibility of 753 non-Enterobacteriaceae gram-negative organisms to cefuroxime compared with that of cephalothin*

Organism (no.)	MIC (cefuroxime/cephalothin)[a] needed for given % of isolates		
	25	50	90
Acinetobacter calcoaceticus			
var. *anitratus* (58)	9.2/>32	17/>32	>32/>32
var. *lwoffii* (16)	3.6/6.6	>32/>32	>32/>32
Aeromonas hydrophilia (5)	<1.0/7.0	1.4/>32	3.0/>32
Haemophilus influenzae (180)	<0.5/1.5	0.6/2.5	2.0/6.6
Haemophilus species (10)	<0.5/0.8	<0.5/1.9	1.4/5.2
Moraxella species (23)	<0.5/2.2	2.0/7.0	32/32
Pseudomonas aeruginosa (393)	>32/>32	>32/>32	>32/>32
Pseudomonas species[b] (57)	>32/>32	>32/>32	>32/>32
Others[c] (12)	0.5/1.0	2.5/5.2	32/32

[a] MIC values (micrograms per milliliter) derived from log-probit plots.

[b] Includes *P. stutzeri* (24), *P. fluorescens* (15), *P. maltophilia* (12), *P. fragii* (3), and one strain each of *P. cepacia*, *P. putrefaciens*, and *Pseudomonas* species NOS.

[c] Includes *Bordetella bronchiseptica* (3), group 11K type 1 (2), *Pasteurella multocida* (4), and one strain each of *Achromobacter xyloseoxidans*, group 11f, and *Alkaligenes* species.

TABLE 3. *Comparison of cefuroxime and cephalothin MICs against 1,334 clinical gram-positive cocci and 25 N. meningitidis isolates*

Organism (no.)	MIC (cefuroxime/cephalothin)[a] needed for given % of isolates		
	25	50	90
Staphylococcus aureus (639)	0.62/0.11	0.82/0.14	1.4/0.23
S. epidermidis (208)	0.17/0.10	0.30/0.20	0.98/0.72
Streptococcus agalactiae (43)	<0.06/<0.06	<0.06/<0.06	0.30/2.7
S. pyogenes (19)	<0.06/<0.06	<0.06/<0.06	0.10/<0.06
Streptococcus species beta-hemolytic not group A, B, or D (138)	<0.06/<0.06	<0.06/<0.06	0.45/0.24
S. pneumoniae (25)	<0.06/<0.06	<0.06/<0.06	0.18/1.5
S. viridans group (31)	<0.06/<0.06	0.10/0.13	>4/1.7
S. faecalis (193)	>4/>4	>4/>4	>4/>4
S. faecium (17)	>4/>4	>4/>4	>4/>4
Other streptococci (21)[b]	<0.06/0.125	0.21/1	>4/>4
N. meningitidis (25)	<0.06/0.16	<0.06/0.22	>4/>4

[a] MIC values (micrograms per milliliter) derived from log-probit plots.

[b] Includes 19 gamma-hemolytic streptococci (not group A, B, or D) and three strains each of *S. bovis* and *S. durans*.

than cephalothin. This was particularly true for *S. agalactiae* (Lancefield group B) and *S. pneumoniae*. Comparable cumulative percentage data were found for all other tested *Streptococcus* species.

Cefuroxime demonstrated a marked antimicrobial activity against *N. meningitidis* strains. Seventy-two percent of the tested isolates was inhibited at 0.06 μg/ml or less.

Table 4 shows the percent susceptibility of strict anaerobic clinical isolates to increasing concentrations of cefuroxime. Only 21% of 34 *Bacteroides fragilis* strains were inhibited by 32 μg of cefuroxime per ml. The other tested anaerobic bacteria showed varying degrees of susceptibility to cefuroxime.

DISCUSSION

This study compared the antimicrobial activity of a new parenteral cephalosporin, cefuroxime, with that of cephalothin on a large number of clinical bacterial isolates from three geographic areas. Several reports have noted that cefuroxime has a more active gram-negative spectrum, particularly among the *Enterobacteriaceae* and *Neisseria* species (2, 6–8, 10).

Seven commonly encountered bacterial species were subjected to statistical analysis. The Kalmogorov-Smirnov two-sample test of significance was used to compare the susceptibility of these organisms to cefuroxime and cephalothin. *Enterobacter aerogenes*, *E. cloacae*, and *S.*

TABLE 4. *Cefuroxime MIC results for 84 clinical anaerobic isolates*

Organism (no.)	Cumulative inhibition (%) at MIC of:			
	0.5	2	8	32
B. fragilis (34)			6	21
Clostridium species[a] (30)	67	87	97	100
Gram-positive cocci[b] (9)	44	89	100	
Bacteroides and *Fusobacterium* species (5)	80	100		
Gram-positive nonsporulating bacilli[c] (4)	75	100		
Eubacterium species (2)				100

[a] Includes *Clostridium perfringens* (21), *C. ramosum* (3), *C. butyricum* (2), and one isolate each of *C. septicum, C. paraputrificum, C. oroticum,* and *C. lentoputrescens.*

[b] Includes *Peptococcus asaccharolyticus* (2) and *P. variabilis* (2), and one isolate each of *Peptostreptococcus intermedius, P. anaerobius, Peptococcus magnus, P. morbillorum,* and *Ruminococcus bromii.*

[c] Includes *Propionibacterium acnes* (2), *Lactobacillus acidophilus* (1) and *Lactobacillus* species (1).

marcescens were significantly ($P = <0.001$) more susceptible to cefuroxime at all tested concentrations (≤ 32 μg/ml). Moreover, equally significant cefuroxime antimicrobial activity was demonstrated against *E. coli, K. pneumoniae,* and *P. mirabilis* up to concentrations of 16, 4, and 8 μg/ml, respectively. Cephalothin was more active than cefuroxime ($P = <0.001$) against the *S. aureus* isolates at concentrations of $\leqq 1$ μg/ml. In addition, no statistically significant susceptibility differences were encountered among collaborating institutions. Like other cephalosporin antimicrobial agents, cefuroxime appears to have a limited spectrum against *P. aeruginosa, Pseudomonas* species, *Enterococci,* and *B. fragilis* (1, 11).

This study of 5,887 clinical bacterial isolates confirms the broad antimicrobial spectrum and activity of cefuroxime as compared with cephalothin. These in vitro features coupled with a 33% serum protein binding, mean effective dose values in experimental animals, dose-related volume distribution, high recovery from urine, and favorable human pharmacokinetics favor further in vivo investigations. Of particular value may be its use against *Neisseria* species due to very low MICs and its high resistance to beta-lactamase hydrolysis (9).

LITERATURE CITED

1. **Ernst, E. C., S. Berger, M. Barza, N. V. Jacobus, and F. P. Tally.** 1976. Activity of cefamandole and other cephalosporins against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. 9:852–855.
2. **Eykyn, S., C. Jenkins, A. King, and I. Phillips.** 1976. Antibacterial activity of cefuroxime, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin, and cefamandole. Antimicrob. Agents Chemother. 9:690–695.
3. **Foord, R. D.** 1976. Cefuroxime: human pharmacokinetics. Antimicrob. Agents Chemother. 9:741–747.
4. **Fuchs, P. C.** 1975. The replicator method for identification and biotyping of common bacterial isolates. Lab. Med. 6:6–11.
5. **Jones, R. N., and P. C. Fuchs.** 1976. Identification and antimicrobial susceptibility of 250 *Bacteroides fragilis* subspecies tested by broth microdilution methods. Antimicrob. Agents Chemother. 9:719–721.
6. **Norrby, R., J.-E. Brorsson, and S. Seeburg.** 1976. Comparative study of the in vitro antibacterial activity of cefoxitin, cefuroxime, and cephaloridine. Antimicrob. Agents Chemother. 9:506–510.
7. **O'Callaghan, C. H., R. B. Sykes, A. Griffiths, and J. E. Thornton.** 1976. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. Antimicrob. Agents Chemother. 9:511–519.
8. **O'Callaghan, C. H., R. B. Sykes, D. M. Ryan, R. D. Foord, and P. W. Muggleton.** 1976. Cefuroxime—a new cephalosporin antibiotic. J. Antibiot. 1:29–37.
9. **Richmond, M. H., and S. Wotton.** 1976. Comparative study of seven cephalosporins: susceptibility to beta-lactamases and ability to penetrate the surface layers of *Escherichia coli.* Antimicrob. Agents Chemother. 10:219–222.
10. **Ryan, D. M., C. H. O'Callaghan, and P. W. Muggleton.** 1976. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. Antimicrob. Agents Chemother. 9:520–525.
11. **Tally, F. P., N. V. Jacobus, J. G. Bartlett, and S. L. Gorbach.** 1975. Susceptibility of anaerobes to cefoxitin and other cephalosporins. Antimicrob. Agents Chemother. 7:128–132.