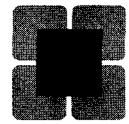

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In vitro comparison of activity of cefixime with activities of other orally administered antimicrobial agents

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■ Cefixime, cefuroxime, cephalexin, cefaclor, penicillin, ampicillin, amoxicillin alone and combined with clavulanate, erythromycin, and trimethoprim/sulfamethoxazole were tested in vitro against nearly 1,100 clinical isolates of bacteria. Minimal inhibitory concentrations (MICs) of > 32 μg/mL were observed for all cephalosporins against > 90% (MIC_{90}) of isolates of *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Morganella morganii*, *Acinetobacter anitratus*, and *Pseudomonas* sp. An MIC_{90} of ≤ 0.25 μg of cefixime per mL was observed with nonenterococcal streptococci, *Klebsiella* sp, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Salmonella* sp, and *Shigella* sp. The MIC_{90} values of cefuroxime and amoxicillin/clavulanate were, respectively, > 32 and 16 μg/mL for *Klebsiella oxytoca*, 4 and 32 μg/mL for *Klebsiella pneumoniae*, 2 and 1 μg/mL for *P mirabilis*, and > 32 μg/mL for *P stuartii*. The MIC_{90} values of cefixime, cefuroxime, amoxicillin/clavulanate, and trimethoprim/sulfamethoxazole were, respectively, 0.12, 2, 0.12, and ≤ 0.5 μg/mL for *Branhamella catarrhalis* and 0.25, 4, 8, and 4 μg/mL for *Haemophilus influenzae*. Overall, trimethoprim/sulfamethoxazole was the most active compound, followed by cefixime.

□ INDEX TERM: ANTIBIOTICS, LACTAM □ CLEVE CLIN J MED 1988; 55:477–482

CEFIXIME [(6R,7R)-7-[(Z)-2-(2-amino-4-thiazolyl)-2-(carboxymethoxyimino)-acetamido]-8-vinyl-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylic acid] is a new orally administered cephalosporin that has ß-lactamase stability and an in vitro spectrum of activity similar to that of third-generation cephalosporins.[1–3]

The objective of this study was to compare the activity of cefixime with that of other orally administered antimicrobials including ampicillin, amoxicillin, amoxicillin/clavulanic acid, penicillin, cefaclor, cephalexin, cefuroxime (the orally administered axetil ester of which is currently in clinical trials), erythromycin, and trimethoprim/sulfamethoxazole (TMP-SMX).

Department of Microbiology, The Cleveland Clinic Foundation.
Submitted for publication Nov 1987; accepted Jan 1988.

This project was supported by a grant from Lederle Laboratories.

MATERIALS AND METHODS

Fresh and stock clinical bacterial isolates from cultures of blood, respiratory secretions, urine specimens, and wounds of in- and out-patients seen at The Cleveland Clinic Foundation were selected for testing. Fresh clinical isolates were tested on a consecutive basis between March and July 1987, and stock clinical isolates were used to supplement species represented by few fresh isolates.

Minimal inhibitory concentrations (MICs) were de-

TABLE 1
COMPARISON OF IN VITRO ACTIVITY OF CEFIXIME WITH OTHER ANTIMICROBIAL AGENTS*

Organisms	Number tested	Cefixime	Cefuroxime	Cephalexin	Cefaclor	Penicillin	Ampicillin	Amoxicillin	Amoxicillin/ Clavulanate†	Erythromycin	Sulfamethoxazole/ Trimethoprim‡
Citrobacter diversus	18										
MIC range		≤0.06–0.25	0.5–>32	4–32	0.5–>32	—	2–>32	>32	0.5–>32	—	≤0.5
MIC_{50}		≤0.06	4	4	4	—	>32	>32	2	—	≤0.5
MIC_{90}		0.25	16	32	32	—	>32	>32	32	—	≤0.5
Citrobacter freundii	58										
MIC range		≤0.6–>32	0.5–>32	4–32	0.5–>32	—	0.5–>32	0.5–>32	0.5–>32	—	≤0.5–>16
MIC_{50}		>32	>32	>32	>32	—	>32	>32	>32	—	≤0.5
MIC_{90}		>32	>32	>32	>32	—	>32	>32	>32	—	>16
Enterobacter aerogenes	65										
MIC range		≤0.06–>32	0.5–>32	16–>32	8–>32	—	8–>32	32–>32	32–>32	—	≤0.5
MIC_{50}		2	8	>32	>32	—	>32	>32	>32	—	≤0.5
MIC_{90}		>32	>32	>32	>32	—	>32	>32	>32	—	≤0.5
Enterobacter cloacae	103										
MIC range		≤0.06–>32	1–>32	4–>32	16–>32	—	4–32	8–>32	8–>32	—	≤0.5–>16
MIC_{50}		4	16	>32	>32	—	>32	>32	>32	—	≤0.5
MIC_{90}		>32	>32	>32	>32	—	>32	>32	>32	—	≤0.5
Escherichia coli	136										
MIC range		≤0.06–>32	0.25–>32	2–>32	0.25–>32	—	0.25–>32	0.12–>32	≤0.06–>32	—	≤0.5–>16
MIC_{50}		0.25	2	8	2	—	4	4	4	—	≤0.5
MIC_{90}		32	16	>32	>32	—	>32	>32	>32	—	≤0.5
Klebsiella oxytoca	30										
MIC range		≤0.06–8	0.25–>32	2–>32	0.25–>32	—	16–>32	16–>32	0.5–>32	—	≤0.5
MIC_{50}		≤0.06	1	4	0.5	—	>32	>32	2	—	≤0.5
MIC_{90}		≤0.06	8	32	16	—	>32	>32	32	—	≤0.5
Klebsiella pneumoniae	88										
MIC range		≤0.06–1	0.5–32	0.5–>32	0.25–32	—	8–>32	2–>32	0.5–>32	—	≤0.5–>16
MIC_{50}		≤0.06	2	4	0.5	—	32	>32	2	—	≤0.5
MIC_{90}		≤0.6	4	8	2	—	>32	>32	32	—	≤0.5
Morganella morganii	41										
MIC range		≤0.06–>32	4–>32	32–>32	>32–>32	—	16–>32	32–>32	32–>32	—	≤0.5–>16
MIC_{50}		2	>32	>32	>32	—	>32	>32	>32	—	≤0.5
MIC_{90}		>32	>32	>32	>32	—	>32	>32	>32	—	≤0.5
Proteus mirabilis	62										
MIC range		≤0.06–8	0.25–16	4–>32	0.5–>32	—	0.5–>32	0.25–>32	0.25–>32	—	≤0.5–>16
MIC_{50}		≤0.06	1	8	1	—	1	1	0.5	—	≤0.5
MIC_{90}		≤0.06	2	16	2	—	2	1	1	—	≤0.5
Proteus vulgaris	21										
MIC range		≤0.06–>32	8–>32	16–>32	16–>32	—	32–>32	>32	1–>32	—	≤0.5
MIC_{50}		≤0.06	>32	>32	>32	—	>32	>32	8	—	≤0.5
MIC_{90}		0.12	>32	>32	>32	—	>32	>32	>32	—	≤0.5

TABLE 1 – continued
COMPARISON OF IN VITRO ACTIVITY OF CEFIXIME WITH OTHER ANTIMICROBIAL AGENTS*

Organisms	Number tested	Cefixime	Cefuroxime	Cephalexin	Cefaclor	Penicillin	Ampicillin	Amoxicillin	Amoxicillin/ Clavulanate†	Erythromycin	Sulfamethoxazole/ Trimethoprim‡
Providencia rettgeri	17										
MIC range		≤0.06–2	≤0.06–>32	2–>32	0.25–>32	—	0.5–>32	2–>32	4–>32	—	≤0.5–>16
MIC_{50}		≤0.06	0.25	>32	>32	—	32	>32	32	—	1
MIC_{90}		0.5	>32	>32	>32	—	>32	>32	>32	—	>16
Providencia stuartii	14										
MIC range		≤0.06–0.5	≤0.06–16	4–>32	0.5–>32	—	0.5–>32	4–>32	1–32	—	≤0.5–>16
MIC_{50}		≤0.06	0.5	>32	>32	—	>32	>32	32	—	>16
MIC_{90}		0.12	4	>32	>32	—	>32	>32	>32	—	>16
Serratia marcescens	58										
MIC range		≤0.06–>32	8–>32	32–>32	16–>32	—	2–>32	2–>32	4–>32	—	≤0.5–>16
MIC_{50}		0.5	>32	>32	>32	—	>32	>32	>32	—	≤0.5
MIC_{90}		16	>32	>32	>32	—	>32	>32	>32	—	1
Streptococcus	50										
Groups A,B,C,F,G											
MIC range		≤0.06–0.25	≤0.06	<0.06–4	≤0.06–0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06–8	≤0.5
MIC_{50}		≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.5
MIC_{90}		0.25	≤0.06	2	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.5
Streptococcus pneumoniae	12										
MIC range		≤0.06–0.5	≤0.06–0.25	≤0.6–8	≤0.06–0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06–0.25	≤0.5–2
MIC_{50}		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.5
MIC_{90}		2	≤0.06	2	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.5
Branhamella catarrhalis	17										
MIC range		≤0.06–0.25	0.12–2	0.12–4	0.12–4	≤0.06–16	≤0.06–4	≤0.06–4	≤0.06–0.12	0.12–5	≤0.5
MIC_{50}		≤0.06	1	2	1	4	1	1	≤0.06	0.12	≤0.5
MIC_{90}		0.25	2	4	2	16	4	4	0.12	0.5	≤0.5
Haemophilus influenzae	23										
MIC range		≤0.06–4	≤0.06–16	2–>32	0.5–>32	—	0.06–>32	0.12–>32	0.12–8	0.5–8	≤0.5–4
MIC_{50}		≤0.06	0.5	8	2	—	8	8	0.5	4	≤0.5
MIC_{90}		0.25	4	>32	16	—	32	32	8	8	4
Staphylococcus aureus	10										
MIC range		8–32	1–2	2–8	2–32	1–>16	2–>32	1–>32	0.5–4	≤0.06–0.12	≤0.5
MIC_{50}		16	2	4	4	4	4	4	1	0.12	≤0.5
MIC_{90}		16	2	4	8	>16	32	16	2	0.12	≤0.5
Staphylococcus	27										
coagulase-neg.											
MIC range		2–>32	0.12–>32	1–>32	1–>32	≤0.06–>16	≤0.06–>32	0.06–>32	0.06–32	≤0.06–>8	0.5–>16
MIC_{50}		16	0.5	16	8	4	8	8	1	>8	2
MIC_{90}		>32	>32	>32	>32	>16	>100	>32	>32	>8	>16

* MIC = Minimal inhibitory concentration in μg/mL; MIC_{50} = MIC for 50% of isolates; MIC_{90} = MIC for 90% of isolates.
† MIC listed expresses amoxicillin activity (combined on a 2:1 basis with clavulanate).
‡ MIC listed expresses trimethoprim activity (combined on a 1:20 basis with sulfamethoxazole).

TABLE 2
ACTIVITY OF CEFIXIME AGAINST SPECIES REPRESENTED BY <10 ISOLATES

Organism (no.)	MIC (μg/mL) for individual isolates
Acinetobacter lwoffii (5)	1, 2, 4(2), 32
Alcaligenes odorans (2)	2, 4
Alcaligenes xylosoxidans (1)	>32
Cedecea sp (1)	0.5
Cedecea neteri (4)	0.125, 0.25, 0.5 (2)
Citrobacter amalonaticus (1)	≤0.06
Enterobacter agglomerans (3)	0.25, 1
Haemophilus parainfluenzae (1)	≤0.06
Hafnia alvei (1)	>32
Providencia alcalifaciens (1)	≤0.06
Salmonella sp (9)	≤0.06(6), 0.125(3)
Serratia liquefaciens (8)	≤0.06(2), 0.125(3), 0.25(2), >32
Serratia odorifera (1)	≤0.06
Serratia rubidaea (1)	0.125
Shigella dysenteriae (1)	0.125

termined according to the microdilution methods and controls recommended by the National Committee for Clinical Laboratory Standards in which approximately 5 x 10^5 colony forming units (CFU)/mL were inoculated into a $\log_2$ progression of concentrations of each antimicrobial that was incorporated in cation-supplemented Mueller-Hinton broth.[4] Studies with 10^7 CFU of seven isolates of ß-lactamase-positive isolates of *H influenzae* and 10 ß-lactamase-positive isolates of *Staphylococcus aureus* per mL were performed to determine inoculum effects on MICs of cefixime and cefuroxime. The ranges of concentrations of antimicrobials tested were as follows: cephalosporins, 0.06–32 μg/mL; ampicillin and amoxicillin alone and when combined in a 2:1 ratio with clavulanate, 0.06–32 μg/mL; penicillin, 0.06–16 μg/mL; erythromycin, 0.06–8 μg/mL; and trimethoprim, 0.5–16 μg/mL combined in a 1:20 ratio with sulfamethoxazole.

RESULTS

A total of 1,096 freshly collected and stocked clinical isolates was tested. Listed in *Table 1* are the ranges of MICs and the MICs for 50 and 90% of isolates for species represented by at least 10 isolates. Listed in *Table 2* are the MICs of cefixime for species represented by fewer than 10 isolates. Among cephalosporins tested, cefixime, followed by cefuroxime, was the most active against the Enterobacteriaceae, although the MIC_{90} values of both cephalosporins against isolates of *Citrobacter freundii*, *Enterobacter* sp, and *Morganella morganii* were > 32 μg/mL. Cefixime was generally inactive against *Acinetobacter anitratus*, *Pseudomonas aeruginosa*, and *Pseudomonas maltophilia* (data not shown). The MIC ranges and MIC_{90} values of amoxicillin/clavulanate closely paralleled those of cefixime and cefuroxime against the Enterobacteriaceae, *B catarrhalis*, and *H influenzae*; however, the MIC_{50} values of cefixime were substantially lower (generally 3 to 5 $\log_2$ dilutions) than those of cefuroxime and amoxicillin/clavulanate against the Enterobacteriaceae. The activities of amoxicillin/clavulanate and cefixime against *B catarrhalis* and *H influenzae* were virtually identical. The most active compound overall against the Enterobacteriaceae was the combination of TMP-SMX. TMP-SMX was also active against *B catarrhalis*.

Inoculum effects on the activities of cefixime and cefuroxime were tested with inocula of 5 x 10^5 CFU/mL and 5 x 10^7 CFU/mL of 7-ß-lactamase-producing *H influenzae*. MICs of each antimicrobial agent remained unchanged in five instances and increased ≥ 5-fold in two instances. No inoculum effects on the activities of cefixime and cefuroxime were noted in studies of 5 x 10^5 CFU/mL and 5 x 10^7 CFU/mL of 10-ß-lactamase-producing *S aureus*.

All antimicrobials tested were active against nonenterococcal streptococci. Most staphylococci tested were penicillin-resistant (MIC > 0.12 g/mL) and, therefore, resistant to ampicillin and amoxicillin. Cefuroxime, cephalexin, amoxicillin/clavulanate, erythromycin, and TMP-SMX were the most active antimicrobials against *S aureus*. None of the antimicrobials tested were consistently active against coagulase-negative staphylococci. Cefixime was generally inactive against staphylococci.

DISCUSSION

The α-methoxyimino aminothiazole side chain at the 7-position of the cephem nucleus is shared by cefixime, cefotaxime, ceftizoxime, and cefmenoxime; it provides enhanced stability to plasmid and chromosomal ß-lactamases and enhanced affinity for target enzymes (penicillin-binding proteins) relative to first-generation cephalosporins.[1–3] Thus, cefixime has a substantially broader spectrum of activity against gram-negative bacteria, including *H influenzae* and *B catarrhalis*, than do currently available orally absorbed cephalosporins, such as cephalexin and cefaclor. Although cefixime is generally more active than cefuroxime and ampicillin/clavulanate on a weight for weight basis, the spectrum of activity of these three antimicrobial agents is very similar. This similarity exists because neither cefixime nor cefuroxime

is hydrolyzed by plasmid-mediated ß-lactamases and because clavulanic acid inactivates plasmid-mediated ß-lactamases.[2,3]

Conversely, since clavulanic acid does not inactivate the type I chromosomally mediated ß-lactamase, which is most notably produced by *C freundii*, *Enterobacter* sp, *Serratia marcescens*, *M morganii*, and *P aeruginosa*, and since mutants of these species that are derepressed for the type I ß-lactamase slowly hydrolyze second- and third-generation cephalosporins,[5] it is not surprising that amoxicillin/clavulanate, cefuroxime, and cefixime exhibited poor activity against our isolates of *C freundii*, *Enterobacter* sp, *M morganii*, and *S marcescens*. The MIC_{90} values for all three antimicrobials against these species were, with a single exception, > 32 µg/mL. The frequency of resistance of our isolates of *C freundii*, *Enterobacter* sp, *M morganii*, and *S marcescens*, as well as of Protereae other than *P mirabilis*, to ampicillin/clavulanate and cefuroxime is in accord with that reported by others,[2,6,7] while that to cefixime is in accord with that reported by Neu et al[2] and Utsui et al[7] but is higher than that reported by Fuchs et al,[3] Mulligan and Kwok,[8] and Tanaka et al.[6] As reported by others,[1,3,7] cefixime, cefuroxime, and amoxicillin/clavulanate were active against ß-lactamase-producing isolates of *H influenzae* and *B catarrhalis*. With the exceptions of *Klebsiella pneumoniae* and *Proteus mirabilis*, other gram-negative bacilli were generally resistant to cephalexin and cefaclor, and gram-negative bacilli other than *P mirabilis* were largely resistant to amoxicillin and ampicillin. Overall, the most active antimicrobial agent tested against gram-negative bacteria was TMP-SMX, resistance to which was limited to *Providencia* sp and *H influenzae*.

Although active against nonenterococcal streptococci, cefixime had, as also reported by others,[1–3,7] little activity against staphylococci. All strains of *S aureus* tested were penicillinase producers and were, therefore, resistant to the penicillins but susceptible to amoxicillin/clavulanate, cephalosporins other than cefixime, TMP-SMX, and erythromycin. None of the antimicrobials tested were particularly active against coagulase-negative staphylococci.

Peak serum levels of cefixime have been reported to be in the range of 3.85 ± 0.23 µg/mL to 4.92 ± 0.51 µg/mL following an oral dose of 400 mg in healthy subjects.[9,10] Thus, it has been proposed that bacteria inhibited by ≤1 µg/mL of cefixime per mL be considered susceptible and that those with MICs of ≥4 µg/mL be considered resistant.[3] The corresponding MIC equivalents of susceptibility and resistance for all cephalosporins other than cefoperazone are ≤8 µg/mL and ≥32 µg/mL, respectively[4]; however, since peak levels of cefuroxime average 8.6 µg/mL following a 500-mg oral dose of the axetil ester,[11] the MIC equivalents of susceptibility and resistance for this compound will likely be reduced somewhat.

Because of the considerable variation in peak cefuroxime levels (4.5 µg/mL to 12.8 µg/mL) following a 500-mg oral dose of the axetil ester[11] and the high relapse rate of women treated with cefuroxime axetil for recurrent bacteriuria,[12] it may be advisable to set the MIC equivalents for susceptibility and resistance of the axetil ester at the same concentrations as those proposed for cefixime. If this were to be the case, few gram-negative bacteria tested in our laboratory would be considered susceptible to cefuroxime axetil, and the oral antimicrobials of choice in descending order of activity would be TMP-SMX, cefixime, and amoxicillin-clavulanate. Ultimately, however, the role of cefixime in the treatment of urinary tract infections must be assessed in clinical trials similar to those carried out with cefuroxime axetil by Brumfitt et al[12] and must be compared with that of TMP-SMX, which exhibits broader activity in vitro and has a well-established record in the treatment of bacteriuria.

In conclusion, cefixime is a novel third-generation oral cephalosporin with activity against nonenterococcal streptococci and plasmid-mediated ß-lactamase-producing gram-negative bacteria but with poor activity against staphylococci and chromosome-mediated ß-lactamase-producing gram-negative bacteria. Cefixime is more active than other oral cephalosporins against ß-lactamase-producing strains of *H influenzae* and *B catarrhalis*, the incidence of which has increased in acute otitis media and in acute exacerbations of chronic bronchitis. Whether, however, cefixime will have any advantages over amoxicillin/clavulanate in the treatment of these types of respiratory tract infections remains to be seen. Finally, cefixime would appear to have little application in skin and soft-tissue infections because of its poor antistaphylococcal activity.

ACKNOWLEDGMENTS

Isolates of *Branhamella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* included strains generously provided by Michael Jacobs, MD, PhD, University Hospitals of Cleveland (OH) and Clyde Thornsberry, PhD, Centers for Disease Control, Atlanta, GA.

Cefixime was supplied by Lederle Laboratories; cefuroxime by Glaxo Inc.; penicillin, cephalexin, cefaclor, and erythromycin by Lilly Research Laboratories; amox-

icillin and amoxicillin/clavulanate by Beecham Laboratories; TMP-SMX by Burroughs Wellcome Co.; and ampicillin by Bristol Laboratories.

The authors also gratefully acknowledge Lynne Atkinson for technical assistance in preparing microdilution trays and Estella Stovall for assistance in preparing the manuscript.

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