JOURNAL OF CLINICAL MICROBIOLOGY, Aug. 1987, p. 1570–1571
0095-1137/87/081570-02$02.00/0

Vol. 25, No. 8

Cross Susceptibility and Absence of Cross Resistance to Cefotetan and Cefoxitin

ARTHUR L. BARRY* AND RONALD N. JONES
The Clinical Microbiology Institute, Tualatin, Oregon 97062

Received 7 April 1987/Accepted 8 May 1987

Tests with 2,713 bacterial isolates (members of the family *Enterobacteriaceae* and gram-positive cocci) from 14 laboratories compared cefoxitin MICs with cefotetan MICs. Strains that were susceptible to cefoxitin could be assumed to be susceptible to cefotetan. Over half of the cefoxitin-resistant isolates of the *Enterobacteriaceae* were susceptible to cefotetan.

Cefotetan and cefoxitin are 7-alpha-methoxy cephalosporins which share a characteristic high-grade resistance to hydrolysis by bacterial β-lactamase enzymes (3). Although the two drugs are structurally related, their in vitro activities differ rather significantly (1, 2). Against members of the family *Enterobacteriaceae*, cefotetan is much more active than cefoxitin, but cefoxitin is generally more active against most gram-positive cocci. The pharmacokinetic properties of the two drugs also differ. Levels of cefotetan in blood are elevated, and the elimination half-life is prolonged (5). Because of differences in the achievable levels in blood, the MIC breakpoint which defines the susceptible category for cefotetan is one doubling dilution greater than that for cefoxitin (≤16 μg of cefotetan per ml versus ≤8.0 μg of cefoxitin per ml) (4).

Now that cefotetan has been released for clinical use in the United States, clinical laboratories are being asked to perform susceptibility tests. Unfortunately, some manufacturers of antimicrobial susceptibility testing systems have not yet completed the studies necessary to permit them to incorporate cefotetan into their test systems. Since cefoxitin can be tested in those systems, we wanted to know how accurately cefotetan susceptibility or resistance could be predicted from the results of cefoxitin susceptibility test results. In vitro data were collected from 14 institutions, and cefoxitin MICs were compared with cefotetan MICs. As a result of this evaluation, we propose an interim solution to this problem.

The following investigators contributed data which were added to those generated in our own institute: A. Molavi, Hahnemann Hospital, Philadelphia, Pa.; B. Cunha, Nassau Hospital, Mineola, N.Y.; S. J. Childs, Brookwood Ambulatory Care Center, Birmingham, Ala.; W. Holloway, Medical Center of Delaware, Wilmington; R. Echols, Albany Medical College, Albany, N.Y.; W. G. Wells, Brookwood Medical Center, Birmingham, Ala.; R. M. Snow, Carraway Methodist Medical Center, Birmingham, Ala.; B. Yangco, University of South Florida, Tampa; S. E. Wilson, Harbor UCLA Medical Center, Torrance, Calif.; D. Hemsell, University of Texas Health Science Center, Dallas; H. Sommers, Northwestern University Medical School, Chicago, Ill.; H. Dalton, Medical College of Virginia, Richmond; and D. G. Bobey and W. Sheikh, Stuart Pharmaceuticals, Wilmington, Del.

Each participant performed either broth microdilution tests or agar dilution tests by the procedures outlined by the National Committee for Clinical Laboratory Standards (4). For each strain, cefoxitin and cefotetan MICs were determined at the same time and the two MICs were directly compared.

The 19 species that were evaluated are shown in Table 1. The data are expressed as the median MIC (MIC for 50% of the strains [MIC_{50}]) for each species. Cefotetan MIC_{50}s were ≤8.0 μg/ml for all species other than *Enterobacter cloacae* and *Enterobacter aerogenes*. With cefoxitin, on the other hand, MIC_{50}s were ≤8.0 μg/ml for only 14 of the 19 species. On a weight-to-weight basis, cefotetan was more active than cefoxitin against members of the *Enterobacteriaceae*, but against the gram-positive cocci, cefoxitin was two to four

TABLE 1. In vitro activities of cefotetan and cefoxitin against 2,713 commonly encountered bacterial pathogens: combined data collected from 14 geographically separate laboratories

Genus and species (no. of isolates tested)	MIC (μg/ml) for 50% of isolates	
	Cefotetan	Cefoxitin
Escherichia		
E. coli (351)	≤0.25	2.0
Citrobacter		
C. diversus (80)	≤0.25	4.0
C. freundii (153)	4.0	≥64
Enterobacter		
E. agglomerans (36)	≤0.25	8.0
E. aerogenes (221)	16	≥64
E. cloacae (291)	32	≥64
Klebsiella		
K. pneumoniae (226)	≤0.25	2.0
K. oxytoca (131)	≤0.25	4.0
Serratia		
S. marcescens (189)	2.0	16
Proteus		
P. mirabilis (152)	≤0.25	2.0
P. vulgaris (87)	≤0.25	4.0
Morganella		
M. morganii (151)	1.0	16
Providencia		
P. rettgeri (63)	≤0.25	4.0
P. stuartii (124)	0.5	4.0
Staphylococcus, methicillin susceptible		
S. aureus (200)	8.0	2.0
Other (71)	8.0	2.0
Streptococcus		
S. agalactiae (34)	8.0	4.0
S. pyogenes (78)	2.0	1.0
S. pneumoniae (75)	2.0	1.0

* Corresponding author.

TABLE 2. Prediction of cefotetan susceptibility or resistance from results of microdilution susceptibility tests with cefoxitin

Microorganisms (no. of isolates tested)	Cefoxitin		Cefotetan			Predictive value of cefoxitin category (%)
	Category[a]	No. of test results	No. of test results[a]			
			S	I	R	
Enterobacteriaceae (2,255)	S	1,252	1,243	3	6[b]	99.3[c]
	I	196	194	2	0	
	R	807	434	89	284	35.2[d]
Gram-positive cocci (458)	S	446	437	9	0	98.0[c]
	I	4	4	0	0	
	R	8[e]	0	0	8[e]	100[d]

[a] S, Susceptible; I, intermediate; R, resistant. Categories are based on criteria of the National Committee for Clinical Laboratory Standards (4).

[b] Discrepant strains include two *Serratia marcescens* strains, one *Enterobacter agglomerans* strain, one *E. aerogenes* strain, one *E. cloacae* strain, and one *Providencia stuartii* strain; five of the six discrepancies were reported by one of the 14 contributing laboratories, and confirmation of those test results was not possible.

[c] (Number susceptible to cefotetan/number susceptible to cefoxitin) × 100 = predictive value of cefoxitin susceptibility result.

[d] (Number resistant to cefotetan/number resistant to cefoxitin) × 100 = predictive value of cefoxitin resistance result.

[e] The eight isolates resistant to both drugs were *S. pneumoniae*.

times more potent than cefotetan. We excluded methicillin-resistant staphylococci from our studies because they should be assumed to be resistant to the cephalosporins, regardless of the results of tests with standard methods (4). Twenty methicillin-resistant strains were excluded, and three false-susceptible results were observed with cefoxitin; all twenty strains were appropriately resistant to cefotetan (data not shown). Of the 75 *Streptococcus pneumoniae* strains, 8 were resistant to both cephalosporins; they were also resistant or relatively resistant to benzylpenicillin. The other streptococci were susceptible to both cephalosporins.

The MICs were categorized by applying the interpretive breakpoints of the National Committee for Clinical Laboratory Standards (4); those categories are compared in Table 2. Among the 2,255 enteric bacilli that were tested, 1,252 (55.5%) were susceptible to cefoxitin and 807 (35.8%) were resistant to cefoxitin. Only 196 strains (8.7%) were intermediate in susceptibility to cefoxitin (MIC, 16 μg/ml). Six of the 1,252 cefoxitin-susceptible strains were reported to be resistant to cefotetan. Five of those six aberrant results were reported by 1 of the 14 participants. Unfortunately, the validity of those six tests could not be confirmed. In the past 3 years, we have evaluated both drugs against more than 1,000 enteric bacilli and have never found a strain which was confirmed to be cefoxitin susceptible but cefotetan resistant. The predictive value of a susceptible test with cefoxitin was 99.3%, i.e., 1,243 of 1,252 strains were also susceptible to cefotetan. The same predictive value was calculated when a cefoxitin MIC of ≤16 μg/ml (intermediate or susceptible category) was used to predict cefotetan MICs of ≤16 μg/ml (susceptible category). Among 807 cefoxitin-resistant enteric bacilli, only 284 strains were also resistant to cefotetan (35.2% predictive value). Among the gram-positive cocci that were tested, only eight *S. pneumoniae* isolates were resistant to both drugs. None of the cefoxitin-susceptible strains were resistant to cefotetan; 437 of 446 cefoxitin-susceptible strains were susceptible to cefotetan (98% predictive value).

In summary, when members of *Enterobacteriaceae*, streptococci, or methicillin-susceptible staphylococci are tested, cefoxitin-susceptible strains can be assumed to be susceptible to cefotetan, but cefoxitin-resistant enteric bacilli are not necessarily resistant to cefotetan.

We thank Waheed Sheikh and David G. Bobey for their assistance in gathering much of the data that are summarized in this report.

LITERATURE CITED

1. **Ayers, L. W., R. N. Jones, A. L. Barry, C. Thornsberry, P. C. Fuchs, T. L. Gavan, E. H. Gerlach, and H. M. Sommers.** 1982. Cefotetan, a new cephamycin: comparison of in vitro antimicrobial activity with other cephams, β-lactamase stability, and preliminary recommendations for disk diffusion testing. Antimicrob. Agents Chemother. **22**:859–877.
2. **Jones, R. N., A. L. Barry, P. C. Fuchs, and C. Thornsberry.** 1986. Antimicrobial activity of cefmetazole (CS-1170) and recommendations for susceptibility testing by disk diffusion, dilution, and anaerobic methods. J. Clin. Microbiol. **24**:1055–1059.
3. **Jones, R. N., and H. W. Wilson.** 1983. Antimicrobial activity, beta-lactamase stability and beta-lactamase inhibition of cefotetan and other 7-alpha-methoxy beta-lactam antimicrobials. Diagn. Microbiol. Infect. Dis. **1**:71–83.
4. **National Committee for Clinical Laboratory Standards.** 1985. Approved standard M7-A. Standard methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. National Committee for Clinical Laboratory Standards, Villanova, Pa.
5. **Smith, B. R., J. L. LeFrock, P. T. Thyrum, B. A. Doret, C. Yeh, G. Onesti, A. Schwartz, and J. J. Zimmerman.** 1986. Cefotetan pharmacokinetics in volunteers with various degrees of renal function. Antimicrob. Agents Chemother. **29**:887–893.