Susceptibility of Clinical Isolates of Bacteria to Cefoxitin and Cephalothin

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The susceptibility of 4,929 unselected clinical isolates of bacteria to cefoxitin and cephalothin was determined by the single-disk method, using a computer-associated electronic zone analyzer to obtain, record, and process measurements of sizes of zones of inhibition. Both cefoxitin and cephalothin were effective against most gram-positive strains, including Staphylococcus aureus, S. epidermidis, micrococci, and all streptococci except enterococci. The three strains of Listeria monocytogenes tested were susceptible to cephalothin but resistant to cefoxitin. There was little difference between the cefoxitin and cephalothin susceptibility of Salmonellae, Citrobacter sp., Enterobacter sp., Proteus mirabilis, and Pseudomonas sp. Cefoxitin was more effective then cephalothin against Escherichia coli, Klebsiella sp., Serratia sp., indole-positive Proteus sp., Providence sp., Flavobacter sp., Herellea vaginicola, and Mima polymorpha. Cefoxitin also appeared to exhibit enhanced activity, as compared with cephalothin, against Bacteroides sp. Thus cefoxitin appears to have a very broad antibacterial spectrum which is greater than that of cephalothin, especially against gram-negative strains.

Cefoxitin is a new semisynthetic cephamycin which is highly resistant to β-lactamases from gram-positive and gram-negative bacteria (6). This property certainly accounts for some, but probably not all (6), of the effectiveness of cefoxitin against cephalothin-resistant organisms which has been demonstrated in preliminary studies (2, 6, 9). These studies suggest that cefoxitin has a broader spectrum of activity than cephalothin, but to date this has not been confirmed with tests of cefoxitin susceptibility of a large series of unselected clinical isolates. We have recently had the opportunity to determine the cefoxitin susceptibility of a large number (4,929) of clinical isolates of bacteria submitted to our laboratory for routine testing. Antibiotic susceptibilities were determined by the single-disk method in conjunction with a computer-associated electronic zone analyzer (4). The latter was utilized for performing, storing, and analyzing measurements of zones of inhibition.

MATERIALS AND METHODS

Bacteria used in this study were unselected clinical isolates submitted for antibiotic susceptibility testing in the Bacteriology Laboratory of the Massachusetts General Hospital. For organisms which grew aerobically, testing was performed by the method of Bauer et al. (1). A mechanical method was used to inoculate the test plates (3), and measurements of zones of inhibition were made with a computer-associated electronic zone analyzer (4), which fed readings directly into the house computer for interpretation, storage, and subsequent analysis. Susceptibilities of Bacteroides sp. were determined by the method of Sutter et al. (7). Since these investigators (7, 8) did not report zone size criteria for cephalothin in their studies of anaerobic susceptibility testing, we have derived our own criteria. Our studies of cephalothin by this method have shown that diameters of zones of inhibition of 23 mm or less correlate with minimal inhibitory concentrations (MICs) of 50 μg/ml or greater for cephalothin (resistant), and zone diameters of 31 mm or greater correlate with MICs of 3.12 μg/ml or less (susceptible) (R. C. Moellering, Jr., J. Nagel, and R. H. Rubin, unpublished data). Zones of 24 to 30 mm were therefore considered "intermediate" for cephalothin against Bacteroides sp. in this study.

Cefoxitin disks (30 μg) were furnished by H. Wallick, Merck Institute for Therapeutic Research. Standard 30-μg cephalothin disks (BBL) were used for comparison. The zone diameter interpretations derived for cephalothin (1) were also applied to cefoxitin in determining the percentage of strains susceptible to each antibiotic.

RESULTS

The results of testing 4,929 strains of bacteria are presented in Table 1. There was little difference in the number of strains susceptible to cefoxitin and cephalothin among *Staphylococcus aureus*, *S. epidermidis*, micrococci, and nonenterococcal streptococci. Neither agent was particularly effective against enterococci, although a small percentage of strains were susceptible to cephalothin. Virtually none of the enterococci were susceptible to cefoxitin. The three strains of *Listeria monocytogenes* included in this study were susceptible to cephalothin but resistant to cefoxitin.

There was little difference between the cefoxitin and cephalothin susceptibilities of *Salmonellae*, *Citrobacter* sp., *Enterobacter* sp., *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Among the remaining gram-nega-

TABLE 1. *Susceptibility of clinical isolates of bacteria to cephalothin and cefoxitin*

Strain	No. of strains tested	Percent susceptible to:	
		Cepha-lothin	Cefoxitin
Gram-positive bacteria			
Staphylococcus aureus	607	100	100
S. epidermidis	271	97	94
Micrococci	6	100	100
Enterococci	563	14	1
Nonhemolytic strepto-cocci, (nonenter-ococcal)	47	98	96
Alpha streptococci	52	97	96
Beta streptococci	46	100	96
Listeria monocytogenes	3	100	0
Gram-negative bacteria			
Escherichia coli	1,210	83	96
Salmonellae	24	97	100
Citrobacter sp.	58	47	50
Klebsiella sp.	523	90	96
Enterobacter sp.	198	17	17
Serratia sp.	126	0	61
Proteus mirabilis	279	97	98
P. morganii	65	1	72
P. rettgeri	25	11	88
P. vulgaris	26	8	96
Providence sp.	25	44	96
Pseudomonas aeruginosa	396	0	4
Pseudomonas maltophilia	30	0	7
Flavobacter sp.	16	0	68
Herellea vaginicola	249	0	18
Mima polymorpha	13	46	54
Anaerobes			
Bacteroides sp.	71	1	1

tive bacilli, a larger percentage was susceptible to cefoxitin than to cephalothin. This difference was particularly striking for *Flavobacter* sp., indole-positive *Proteus* sp., *Providence* sp., and *Serratia* sp., among which more than 50% of strains resistant to cephalothin were susceptible to cefoxitin. Although the differences were not as great, cefoxitin was also more effective against *Escherichia coli*, *Klebsiella* sp., *Pseudomonas maltophilia*, *Herellea vaginicola*, and *Mima polymorpha*. Between 6 and 18% of these strains which were resistant to cephalothin were susceptible to cefoxitin.

Among the *Bacteroides* sp., the majority of strains were resistant to both cephalothin and cefoxitin when our original zone size criteria were applied. However, when the data were recalculated using as a criterion for susceptibility a zone diameter of 24 mm or greater (which corresponds to an MIC of 25 μg/ml or less), 44% of the strains were susceptible to cefoxitin as compared with 5% to cephalothin.

Quantitative differences in susceptibility of various organisms to cephalothin and cefoxitin can be shown quite clearly by comparing computer-generated plots of the distribution of zones of inhibition produced by each agent (5).

Figure 1 shows the superimposition of the computer-generated plots of the distribution of zones of inhibition produced by 30-μg cefoxitin and cephalothin disks against *Proteus morganii*. The enhanced activity of cefoxitin against this strain is demonstrated by the fact that the curve for cefoxitin is shifted to the right of that for cephalothin (i.e., cefoxitin produced generally larger zones of inhibition). Similar plots were made for the other organisms tested. To conserve space and to make interpretation easier, a number of these zone size distributions have been converted to line drawings and incorporated in Fig. 2 and 3.

In general, cephalothin produced larger zones than cefoxitin against staphylococci (Fig. 2). The situation was strikingly different for the enterococci, however. Cefoxitin elicited no zone of inhibition (diameter of disk, 6 mm) against 96% of the enterococci, whereas the majority of these organisms were inhibited to a greater or lesser degree by cephalothin. Although the overall patterns of distribution of zones of inhibition for cephalothin and cefoxitin were similar against *E. coli*, the curve for cefoxitin was shifted to the right of that for cephalothin, confirming that a number of strains resistant to cephalothin were susceptible to cefoxitin. The two antibiotics produced nearly identical patterns against *Klebsiella* sp. The zone size distri-
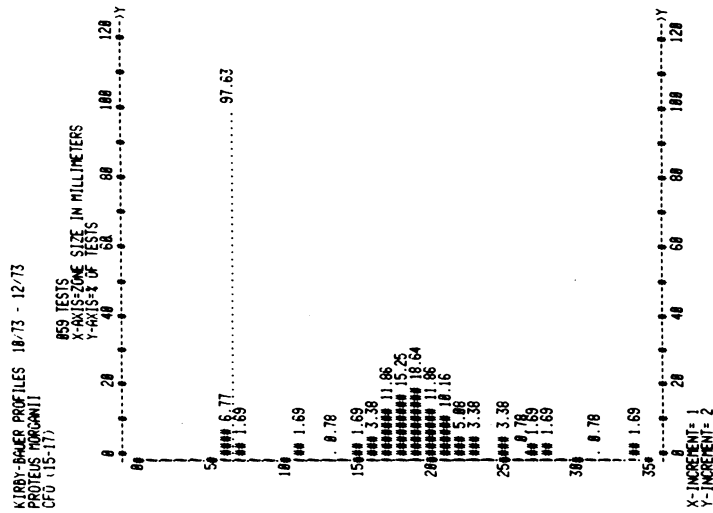
FIG. 1. *Superimposition (slightly out of register) of computer-generated distribution of sizes (diameters) of zones of inhibition for cefoxitin (cross-hatched figures) and cephalothin (dotted lines) against Proteus morganii. Abscissa, zone diameter (mm); ordinate, percentage of strains tested.*
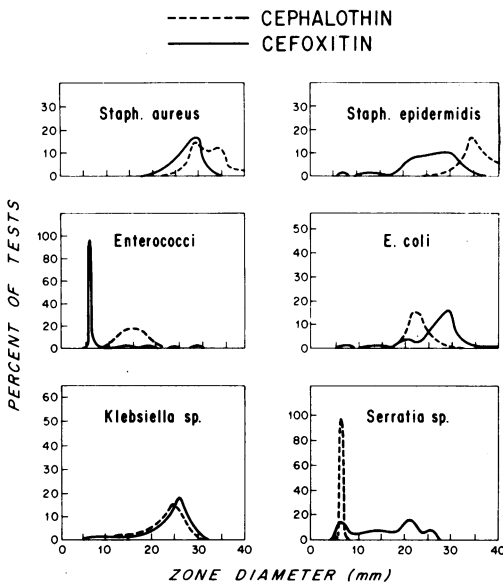

FIG. 2. *Superimposition of distribution of sizes of zones of inhibition for cefoxitin and cephalothin against selected species. Original computer-generated plots similar to those in Fig. 1 have been converted to line drawings.*

FIG. 3. .*Superimposition of distribution of sizes of zones of inhibition for cefoxitin and cephalothin against selected species. Original computer-generated plots similar to those in Fig. 1 have been converted to line drawings.*
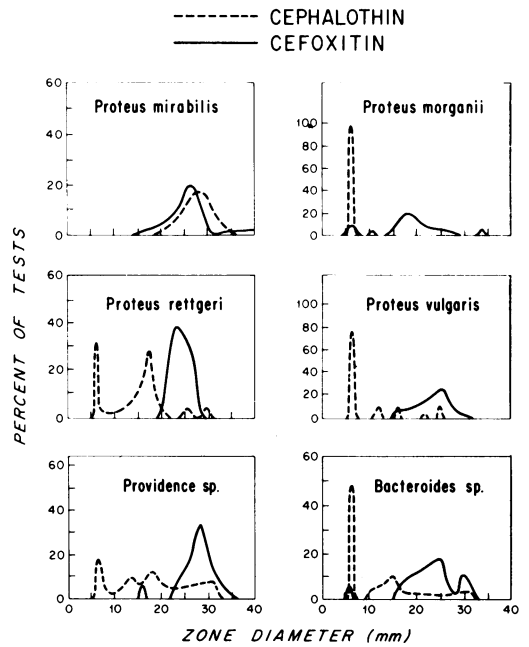
butions similarly revealed that there was little difference between the effectiveness of cephalothin and cefoxitin against *Proteus mirabilis*. However, the markedly increased activity of cefoxitin against all indole-positive *Proteus* strains tested is clearly shown in Fig. 3. Likewise, these distributions of zone diameters illustrate the increased susceptibility of *Providence*

sp., *Serratia* sp., and *Bacteriodes* sp. to cefoxitin as compared with cephalothin.

DISCUSSION

The present studies confirm the in vitro effectiveness of cefoxitin against a wide variety

of unselected clinical isolates of bacteria. Cefoxitin was active against staphylococci and all streptococci except enterococci, although the zones of inhibition among the gram-positive strains were generally larger with cephalothin than with cefoxitin. This suggests that although the majority of strains are susceptible to both agents cephalothin may be more effective against gram-positive strains. The resistance of enterococci to cefoxitin was striking and appeared so consistently that it might prove useful as an additional marker for the presumptive identification of enterococci before the results of serological and biochemical tests for speciation are available. Similar high-level resistance of enterococci to methicillin by disk testing has also been shown in our laboratory (R. C. Moellering, Jr., B. K. Watson, and L. J. Kunz, Amer. J. Med., in press).

Without exception, cefoxitin was equally as effective or more effective than cephalothin against the strains of gram-negative bacilli included in our studies. The enhanced activity of cefoxitin was particularly evident for *Flavobacter* sp., indole-positive *Proteus* sp., *Providence* sp., and *Serratia* sp. In addition, a number of strains of *E. coli*, *Pseudomonas maltophilia*, *H. vaginicola*, *M. polymorphia*, and *Klebsiella* sp. which were cephalothin resistant by single-disk testing were susceptible to cefoxitin. The significance of the increased susceptibility of some strains of *Herellea vaginicola* and *Pseudomonas maltophilia* to cefoxitin is unclear, since only a relatively small total number of these organisms was susceptible. However, the fact that 96% of strains of *E. coli* and *Klebsiella* sp. were cefoxitin susceptible, as compared with 83% and 90% susceptibility to cephalothin, may have clinical importance. We encountered 197 strains of *E. coli* which were cephalothin resistant but susceptible to cefoxitin.

The mechanism of the enhanced effectiveness of cefoxitin seems related, in part, to its marked resistance to hydrolysis by the β-lactamases produced by a number of species of gram-negative bacilli (6). However, this does not appear to be the entire explanation, since Onishi et al. have also shown that there is an intrinsic resistance (or basic tolerance) of certain species · to cefoxitin and cephalothin which is unrelated to their ability to produce β-lactamase (6). This latter property may also contribute to the resistance of a given strain to cephalothin or cefoxitin. Indeed, among certain species of organisms we noted that the general pattern of distribution of sizes of zones of inhibition for

cefoxitin and cephalothin were similar but not superimposed (i.e., one distribution shifted slightly to the right or left of the other). It is possible that these are examples of differences in basic tolerance of such strains to cephalothin and cefoxitin.

Cefoxitin disks produced consistently larger zones of inhibition against our *Bacteroides* sp. (most of which were penicillin-resistant *B. fragilis*) than did cephalothin disks containing equal concentrations of the drug. Using very strict criteria for susceptibility (corresponding to an MIC of 3.12 μg/ml or less), essentially all strains were resistant to both cephalothin and cefoxitin. However, if one utilized somewhat less stringent criteria (corresponding to an MIC of 25 μg/ml or less, levels which can readily be achieved in blood with parenteral cephalothin therapy), almost half of the strains tested were susceptible to cefoxitin. Thus, these studies raise the possibility that cefoxitin may also be active against a significant number of strains of *Bacteroides fragilis*, but further studies using quantitative techniques are necessary to confirm this observation.

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