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Tentative Interpretive Standards for Agar Disk Diffusion Antimicrobial Susceptibility Testing of Cefoperazone

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Cefoperazone is a new cephalosporin with a very wide spectrum of activity, including activity against *Pseudomonas aeruginosa*. It has less activity on enterococci and *Acinetobacter*. Of the 459 selected bacterial strains tested in this study, only 1.5% (7 strains and 6 genera) had minimum inhibitory concentrations of ≥128 μg/ml. For a minimum inhibitory concentration breakpoint of ≤32 μg/ml (susceptible), we recommend that the disk diffusion test be done with a 75-μg disk and breakpoints of ≥18 mm for susceptible, 15 to 17 mm for intermediate, and ≤14 mm for resistant. Diffusion tests using these criteria yielded only 1.1% very major or major errors.

Cefoperazone is a new parenteral piperazine cephalosporin antimicrobial agent that has been demonstrated to have a wide spectrum of antimicrobial activity against medically important bacteria (1, 7–11, 18). Preliminary studies indicate that the drug has very favorable pharmacological properties (2, 5, 12, 17). Therefore, it is possible that this drug could, in the near future, be approved for the treatment of infected patients.

If this antimicrobial agent is approved for therapeutic use, it would be advantageous to have already determined the methods that could be used for antimicrobial susceptibility tests with cefoperazone. Since the agar disk diffusion test (14) is the routine method used in most clinical microbiology laboratories, we have investigated various test parameters to determine whether a disk diffusion test with cefoperazone is feasible and, if so, to establish the most efficacious disk drug concentration and interpretive zone diameter breakpoints. The following is a report of those studies.

MATERIALS AND METHODS

Bacteria. The 459 bacteria used in this study are listed in Table 1. They were selected without regard to the frequency with which they are routinely found in clinical microbiology laboratories, but were chosen to represent typical microbial species found in clinical practice, including both cephalothin-susceptible and cephalothin-resistant strains. These were recent clinical isolates, but were supplemented with stock strains when necessary to achieve the desired species representation. Many of these organisms were selected from those strains sent to one laboratory (C.T.) by six collaborators (A. L. Barry, Sacramento, Calif.; P. C. Fuchs and R. N. Jones, Portland, Ore; T. L. Gavan, Cleveland, Ohio; E. H. Gerlach, Wichita, Kans.; and H. M. Sommers, Chicago, Ill.) from five geographic locations. The selected set of strains was then distributed to each participant.

Disk diffusion tests. The four cefoperazone disk potencies (30, 50, 75, and 100 μg) used in this study were prepared in one laboratory (C.T.) by adding the appropriate concentration of the antimicrobial, contained in 25 μl of diluent, to a 6-mm filter paper disk. The disks were dried and stored at −70°C or below in the presence of silica gel desiccant containing an indicator, and the disks were shipped frozen to the other participants. The disk diffusion tests were performed by the standard method of the National Committee for Clinical Laboratory Standards (14). Standard diffusion curves were performed as described by Barry (3).

Dilution antimicrobial susceptibility tests. The minimum inhibitory concentrations (MICs) for these organisms were determined by the broth microdilution method as described in the National Committee for Clinical Laboratory Standards standard for dilution tests (15). The microdilution trays containing cation-supplemented Mueller-Hinton broth (15) were prepared as a single lot by one manufacturer (Prepared Media Laboratory, Portland, Ore.). They were shipped frozen to each participant, and maintained there at −20°C or below until just before inoculation with the test strains (4, 6).

Statistical methods. The regression coefficients were obtained by computer, using the method of least squares. The tabulation of zones of inhibition and MICs by organism, as well as by the error rate bounding method (13), was also performed by computer, using appropriate programs.

These tests were performed collaboratively in different laboratories, by using the same protocol, as described previously (4, 6, 18). Comparability of results

TABLE 1. Population of bacteria[a] used to develop cefoperazone (T-1551) disk criteria and a comparison of susceptibility to cephalothin

Organism (no.)	No. resistant to cephalothin (≥16 μg/ml) and susceptible to cefoperazone at:		
	≤16 μg/ml	≤32 μg/ml	≤64 μg/ml
Staphylococcus aureus (49)	0	0	0
Streptococcus pneumoniae (20)	0	0	0
Streptococcus pyogenes (19)	0	0	0
Streptococcus faecalis (10)	2	5	3
Acinetobacter species (15)	5	8	1
Pseudomonas aeruginosa (82)	72	7	1
Pseudomonas species (30)	22	3	5
Citrobacter species (20)	9	2	0
Escherichia coli (25)	1	1	0
Enterobacter species (50)	40	0	0
Klebsiella pneumoniae (25)	1	0	0
Proteus mirabilis (25)	0	0	0
Proteus, indole positive[b] (30)	28	1	0
Providencia stuartii (24)	23	1	0
Serratia marcescens (25)	20	4	1
Salmonella species (10)	0	0	0

[a] Of the 459 organisms tested, 186 (40.5%) were susceptible to both cefoperazone and cephalothin at ≤8 μg/ml. Only seven isolates (1.5%) were resistant to cefoperazone at ≥128 μg/ml. These strains were *Salmonella enteritidis* (1 isolate), *Acinetobacter calcoaceticus* subsp. *anitratus* (1), *Pseudomonas aeruginosa* (2), *Citrobacter freundii* (1), *Klebsiella pneumoniae* (1), and *Proteus vulgaris* (1).

[b] Includes 10 strains each of *Proteus vulgaris*, *Morganella morganii*, and *Providencia rettgeri*.

obtained in these laboratories has been repeatedly demonstrated.

RESULTS

A list of the 459 bacteria used in this study and a comparison of their susceptibilities to cefoperazone and cephalothin are shown in Table 1. The greater spectrum of activity of cefoperazone is demonstrated by the facts that 59.5% of the strains were resistant to cephalothin at ≥16 μg/ml and only 9.4% were resistant to cefoperazone at the same concentration. Organisms highly resistant to cefoperazone (MIC, ≥128 μg/ml) were distributed among six genera of gram-negative bacilli. If one examines the cefoperazone MIC_{90} values for all strains, however, they can be stratified as shown in Fig. 1. Most of the enteric bacilli (except *Serratia*) and *Staphylococcus aureus* are very susceptible to cefoperazone. *Pseudomonas aeruginosa* and *Serratia* are slightly less susceptible but are still well within the susceptible range. *Acinetobacter* and enterococci are the least inhibited by cefoperazone. On the other hand, the cephalothin MIC_{90} values in Fig. 2 show the markedly decreased activity of this reference drug against most of the organisms (except *S. aureus*) at the dosages usually administered clinically.

An analysis of the cross-resistance between cefoperazone, cephalothin, cefamandole, and cefoxitin is shown in Table 2. These data indicate the necessity of having a separate cefoperazone disk and that presently available cephalosporin disks cannot serve as a class disk for this new cephalosporin.

Mean zone diameters were also determined for five reference strains, using disks with concentrations of 5 to 200 μg (Table 3). These data, as well as the other diffusion data, indicated that the cefoperazone diffusion characteristics would permit development of a disk diffusion test.

The standard diffusion curves (not shown) for cefoperazone and four reference organisms indicate a greater antimicrobial activity of cefoperazone against *S. aureus*, *Escherichia coli*, and *P. aeruginosa* than against *Streptococcus faecalis*. These data also showed that the cefoperazone rate of diffusion is similar to that of cefamandole.

Regression statistics for 30-, 50-, 75-, and 100-μg disks are presented in Table 4, and the scattergrams for the 30- and 75-μg disks are shown in Fig. 3 and 4. The slopes (−0.30 to −0.32) and correlation coefficients (0.81 to 0.85) are quite similar. If one chooses a breakpoint of ≥18 mm as susceptible, using the method of Metzler and DeHaan (13), the error rates are very low, particularly with the 75-μg disk (major error, 0.7%). If one then applies an intermediate zone of 3 mm as derived from the slope statistics and the lower limit of a short-interval regression line (4 to 256 μg/ml), as previously described (4,

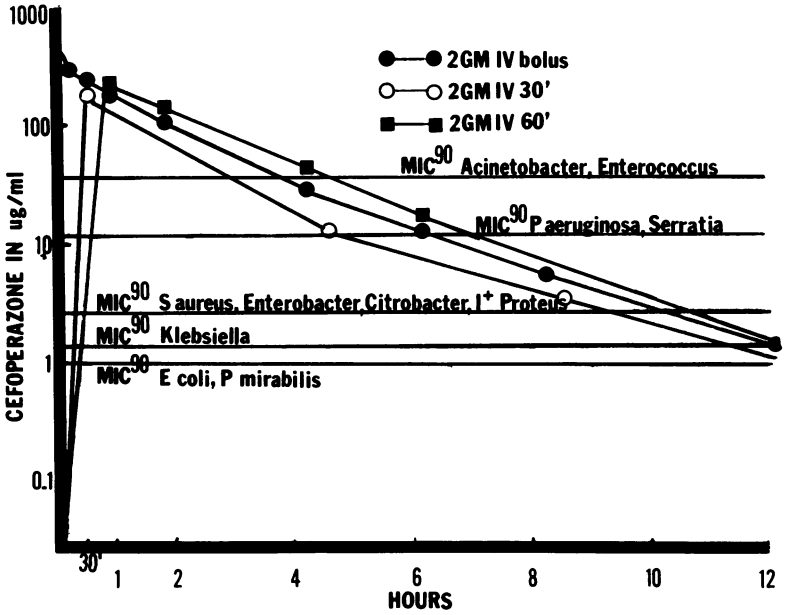

FIG. 1. Serum levels of cefoperazone achieved with 2 g of drug given intravenously (IV) as a bolus or continuously over a period of 30 or 60 min. Also shown are the MIC_{90} values (concentrations at which 90% of the organisms are inhibited) for various clinically important bacteria (5, 9, 12, 17). I^+, Indole positive.

6) and shown in Fig. 5, the error rates were further reduced for both the 30- and 75-μg disks (4, 6).

On the basis of these data, we selected the disk drug concentrations and zone diameter interpretive breakpoints shown in Table 5, in which an intermediate MIC of 32 μg/ml was used with the 30-μg disk and 64 μg/ml was used for the 75-μg disk. The organisms for which major and very major errors were obtained when the 75-μg disk was used are as follows: very major errors—*Citrobacter freundii, Proteus vulgaris,*

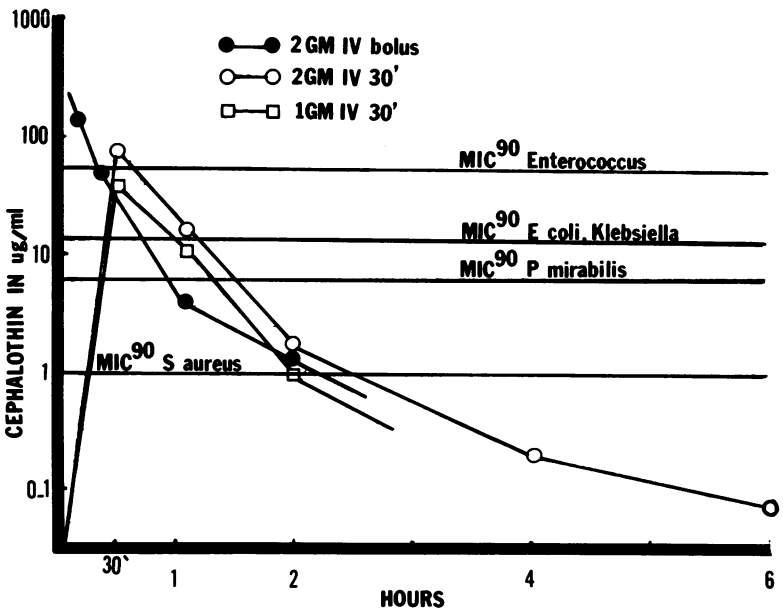

FIG. 2. Serum levels of cephalothin achieved with 2 g of drug given intravenously (IV) as a bolus or continuously over a period of 30 or 60 min. Also shown are MIC_{90} values for various bacteria (6, 8, 9).

TABLE 2. Cross-resistance analysis of the 459 bacteria tested

Cephalosporin	Susceptible MIC (μg/ml)	No. of strains (cephalosporin and resistant MIC)				
		Cefoperazone (≥128 μg/ml)	Cefoperazone (≥32 μg/ml)	Cephalothin (≥16 μg/ml)	Cefamandole (≥16 μg/ml)	Cefoxitin (≥16 μg/ml)
Cefoperazone	≤64			266	194	210
Cefoperazone	≤16			223	151	167
Cephalothin	≤8	0	0		0	0
Cefamandole	≤8	0	2	73		35
Cefoxitin	≤8	2[a]	5	62	25	

[a] One strain each of *Klebsiella pneumoniae* and *Salmonella enteritidis*.

TABLE 3. Mean zone diameters obtained with various cefoperazone disk concentrations and standard reference organisms

Disk potency (μg)	Inhibitory zone diam (mm)				
	S. faecalis ATCC 29212	*S. aureus* ATCC 29213	*S. aureus* ATCC 25923	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853
5	7.2	16.1	21.0	25.8	17.7
10	9.3	18.3	23.0	27.2	22.3
15	12.7	19.7	24.7	28.5	25.2
30	14.7	21.8	26.5	29.4	28.5
50	16.5	23.5	27.6	30.1	30.4
75	18.5	25.0	28.5	30.7	32.2
100	18.5	25.0	29.1	30.5	32.8
150	20.1	25.8	29.4	31.1	34.0
200	21.1	26.6	29.4	32.0	35.6

TABLE 4. Regression line statistics for various disk concentrations of cefoperazone

Cefoperazone disk concn (μg)	Correlation coefficient	Slope	*y* intercept (μg/ml)	Total no. of observations
30	0.85	−0.3005	432	445
50	0.84	−0.3123	765	447
75	0.82	−0.3170	1,073	446
100	0.81	−0.3207	1,412	445

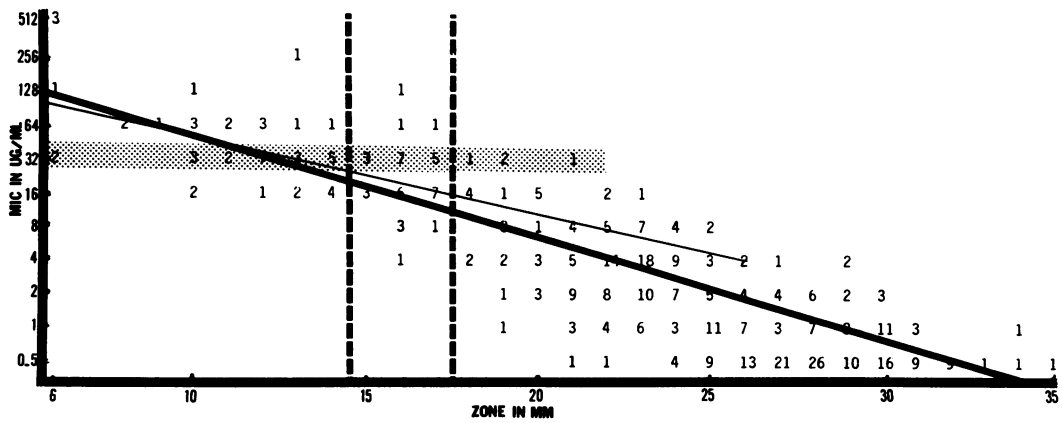

FIG. 3. Regression line plots for all organisms (total, 445), using the 30-μg cefoperazone disk. Vertical broken lines represent the best set of interpretive zones, and the shaded MIC (32 μg/ml) would be representative of the intermediate concentration. Narrow regression line plot is for short-interval analysis of MICs ranging between 4 and 256 μg/ml.

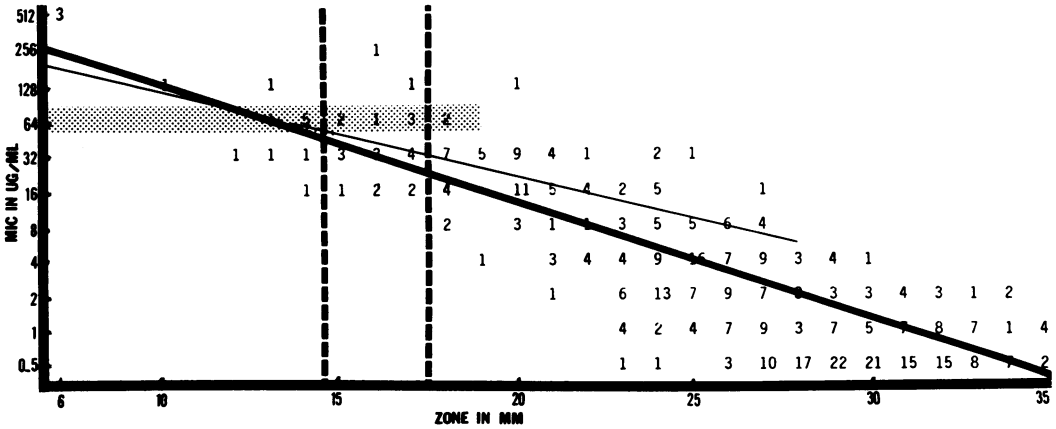

FIG. 4. Regression line plots for all organisms (total, 446), using the 75-μg cefoperazone disk. Vertical broken lines represent the best set of interpretive zones, and the shaded MIC (64 μg/ml) would be representative of the intermediate concentration. Narrow regression line plot is that of the short-interval analysis of cefoperazone MICs ranging from 4 to 256 μg/ml.

and *Pseudomonas cepacia*; major errors—*Acinetobacter anitratus*, *P. aeruginosa*, *S. aureus* (methicillin resistant), and *Streptococcus faecalis*. Error rates were determined by the method of Metzler and DeHaan (13). No particular organisms were involved more than others since seven different species gave the seven discrepant results. With the 75-μg disk, 5% of the organisms had intermediate zone diameters. Species with more than one intermediate result (number in parentheses) were *Acinetobacter* (7), *Streptococcus faecalis* (5), *P. aeruginosa* (2), *Serratia marcescens* (2), and methicillin-resistant *S. aureus* (2), as would be expected from the MIC_{90} data (Fig. 1). Of the 14 intermediate results by MIC (64 μg/ml), 4 were with *Streptococcus faecalis*, more than any other species. The total of 3% of MICs at this intermediate concentration was similar to that observed by Jones et al. from a bacterial population of nearly 9,000 strains (Fig. 5) (8, 9).

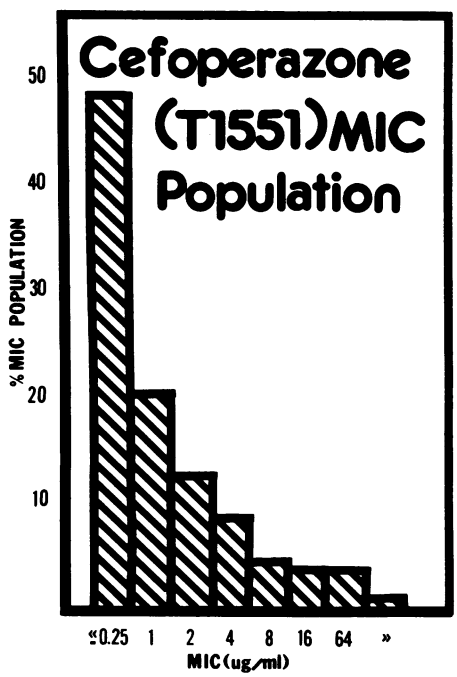

FIG. 5. Cefoperazone MIC population statistics for 8,700 recent clinical isolates; 93.3 and 98.5% of strains were inhibited at ≤16 and ≤64 μg/ml, respectively.

The organisms shown in Table 6 are recommended for control of disk diffusion tests (14). These organisms were tested 20 separate times with the four different cefoperazone disks and the 30-μg cephalothin disk. The modal MICs and ranges of disk inhibitory zone diameters obtained are presented (Table 6).

DISCUSSION

Until recent years, cephalothin was the class disk which represented all cephalosporins in agar disk diffusion antimicrobial susceptibility tests. But when cefoxitin and cefamandole were approved for clinical use it became apparent that the cephalothin disk could no longer represent these two new beta-lactam antimicrobials, and a 30-μg disk for each was thus approved and recommended for use in clinical laboratories (14). An analysis of cross-resistance (Table 2) confirmed the decision to use these two new disks and also showed that cefoperazone must also have its own disk. The recommendations set forth in Table 5 were determined after taking into consideration the antimicrobial spectrum of activity of the new cephalosporin, its pharma-

TABLE 5. Recommendations for interpretive criteria with the 30- and 75-μg cefoperazone disk and the NCCLS method (14)[a]

Disk (μg/ml)	Susceptible MIC (μg/ml)	Zone criteria (mm)		Error rate (%)[b]		
		Susceptible	Resistant	Very major	Major	Minor
75	≤32	≥18	≤14	0.2	0.9	5.4
30	≤16	≥18	≤14	0.0	2.0	11.2

[a] NCCLS, National Committee for Clinical Laboratory Standards.
[b] Z_s was determined by using the method of Metzler and DeHaan (13) and then applying a 3-mm intermediate zone and corresponding intermediate cefoperazone MIC (64 and 32 μg/ml for the 75- and 30-μg disks, respectively).

cology, its agar diffusion characteristics, its molecular characteristics, and statistical evaluation of the in vitro data.

The very wide spectrum of activity of cefoperazone on bacteria commonly associated with clinical infections is shown by the MIC_{90} values depicted in Fig. 1. Of the organisms likely to be tested by disk diffusion, cefoperazone has a marked activity on *Enterobacteriaceae* and *S. aureus* (8, 9), although the activity on the latter species is not as great as that of cephalothin. Unlike other available cephalosporins, cefoperazone also is active on most *P. aeruginosa* strains, with MICs well below the achievable serum levels. *Acinetobacter* and enterococci fall into an intermediate level of susceptibility.

Cefoperazone also has activity on some species that are not usually tested by the disk diffusion method. It is very active against *Haemophilus influenzae* and *Neisseria* species (1), streptococci other than serogroup D (8, 9, 18), and anaerobes (7–10).

A comparison of the spectra of antimicrobial activity of cefoperazone with that of cefotaxime and moxalactam, two other new broad-spectrum beta-lactam antibiotics that have been recently studied (4, 6), showed that they are similar in many ways. The major difference is that cefoperazone has greater activity on *P. aeruginosa* and streptococci (8, 9, 11, 18). It has minimal activity on *Campylobacter* sp., but none of the three is particularly active on this species (M. Miller, J. Swenson, and C. Thornsberry, manuscript in preparation). Although all three cephalosporins are essentially resistant to beta-lactamases, it is probable that cefotaxime and moxalactam are more stable than cefoperazone (16).

The serum levels of cefoperazone achieved with the usual 2-g dose given as a bolus, or over periods of 30 or 60 min, are shown in Fig. 1 (2, 5, 12, 17). It appears that in most cases the drug could be given twice daily and the levels would be adequate to inhibit the enteric bacilli, staphylococci, anaerobes, non-enterococcal streptococci, and many *P. aeruginosa* strains. In addition, the levels in the first 6 h would probably be adequate to suppress many of the *Acinetobacter* and enterococci. The superior pharmacological properties of cefoperazone compared with an older cephalosporin such as cephalothin can be seen by comparing Fig. 1 and 2. At 6 h, the concentration of cephalothin is minimal and would essentially obviate twice daily or thrice daily dosing. Greater serum levels are also obtained with cefoperazone than with cefotaxime and, to lesser extent, moxalactam (2, 4–6, 12). Because of these pharmacological differences, we have chosen a susceptible breakpoint of ≤32 μg/ml (resistant, >64 μg/ml) for cefoperazone, compared with susceptible breakpoints of ≤8 μg/ml (moderately susceptible, 16 to 32 μg/ml; resistant, >32 μg/ml) for cefotaxime and moxalactam (4, 6). These MIC breakpoints are obviously important when choosing a disk drug concentration for the drugs.

TABLE 6. Quality control organism data for cefoperazone and cephalothin disk[a] from 20 tests

Antimicrobial (disk potency, μg)	*E. coli* (ATCC 25922)		*S. aureus* (ATCC 25923)		*P. aeruginosa* (ATCC 27853)	
	MIC mode (μg/ml)	Zone range (mm)	MIC mode (μg/ml)	Zone range (mm)	MIC mode (μg/ml)	Zone range (mm)
Cefoperazone (30)	≤0.5	29–32	1	26–28	4	21–26
Cefoperazone (50)	≤0.5	29–34	1	27–31	4	23–27
Cefoperazone (75)	≤0.5	29–34	1	27–33	4	24–29
Cefoperazone (100)	≤0.5	30–34	1	28–33	4	25–29
Cephalothin (30)	8	18–23	≤0.125	32–35	>64	6

[a] In laboratory-prepared disks.

A study of the effects of various disk masses on diffusion tests (Table 3) showed that the zone diameters gradually increased as the disk antimicrobial concentration increased. When regression lines were plotted on four of these disk concentrations (30, 50, 75, and 100 μg), they were essentially parallel. This is also reflected in the regression statistics in that the slopes do not significantly differ (Table 4).

Molecular weight also contributes to the diffusion characteristics of an antimicrobial agent and ultimately may be a factor in the selection of the disk to be used in a diffusion test. When the molecular weights of the sodium salts of cefoperazone, moxalactam, and cefotaxime are compared, they decrease in that order (667.6, 564.5, and 477.5). Cefoperazone thus has 28.2% fewer active molecules per unit weight than does cefotaxime, with moxalactam in between. By comparison, the molecular weight of cefamandole is 512.5, and that of cephalothin is 418.4. The higher molecular weight is yet another factor which contributed to our selection of a higher disk concentration for cefoperazone than for the other cephalosporin drugs.

The regression lines and regression statistics (Table 4), in addition to the zone diameters themselves (Table 3), indicated that the diffusion rate was adequate for one to assume that a disk diffusion test could be used to discriminate susceptible and resistant strains at MIC breakpoints of 32 μg/ml. When these data were examined by the error rate bounding method of Metzler and DeHaan (13) and the distribution of zone diameters for the population of bacteria used in the study were compared with MICs, we concluded that the breakpoints given in Table 5 would be the most efficacious. On the basis of presently available pharmacological data, we believe that a susceptible MIC breakpoint of 32 μg/ml is the most appropriate and therefore the 75-μg disk mass should be recommended. Using the 75-μg disk and the 14- and 18-mm breakpoints, an accurate interpretation rate of 93.5% was achieved, and only 0.2% of the errors were very major. The random distribution of errors among different organisms is also desirable, since it means the method would not routinely fail to discriminate susceptibility with a particular group of organisms. The number (23 or 5%) and distribution of intermediate disk results (10 genera) were also favorable. More than half the intermediate results were with the organisms that one would predict based on in vitro susceptibility data, i.e., *Acinetobacter*, enterococci, *P. aeruginosa*, and *Serratia marcescens*. Of these 23 strains, 9% had resistant (≥128 μg/ml) MICs, 26% had intermediate MICs (64 μg/ml), and 65% were susceptible by the MIC dilution test.

The three organisms presently recommended for quality control of disk diffusion tests also appear to be useful for control of disk diffusion tests with cefoperazone. The data for these three strains that we have presented here are "preliminary results" intended for interim use only. A more complete study utilizing many more tests in a larger number of laboratories is currently in progress, and these data will be examined by the appropriate statistical techniques to establish definitive recommendations for these quality control parameters. Therefore, if this antibiotic is approved for general use, the appropriate recommendations for quality control can be made at the same time and published in readily available references (14).

In conclusion, cefoperazone is a new cephalosporin with an unusually broad spectrum of activity. We recommend that a susceptible MIC breakpoint of ≤32 μg/ml be used. We further recommend that the cefoperazone disk used in the standard disk diffusion test have a disk drug content of 75 μg and that the interpretive zone diameter breakpoints be ≥18 mm for susceptible, 15 to 17 mm for intermediate, and ≤14 mm for resistant. With this disk drug content and these breakpoints, only 1.1% very major or major errors were obtained with the organisms used in this investigation.

ADDENDUM IN PROOF

Since this manuscript was written, the National Committee for Clinical Laboratory Standards (NCCLS) has adopted the use of a 75-μg disk with the following breakpoints: susceptible, ≥21 mm (≤16 μg/ml); and resistant, ≤14 mm (>64 μg/ml). The NCCLS has also chosen the following quality control criteria: *E. coli* ATCC 25922, 28 to 34 mm; *S. aureus* ATCC 25923, 24 to 33 mm; and *P. aeruginosa*, 23 to 29 mm. (See NCCLS document M2-A2-S2.)

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