Comparison of Ticarcillin and Carbenicillin Activity Against Random and Select Populations of *Pseudomonas aeruginosa*

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The in vitro activities of ticarcillin (T) and carbenicillin (C) against 253 strains of *Pseudomonas aeruginosa* (108 randomly selected clinical isolates and 145 isolates determined to be C resistant by 10 referring hospitals) were evaluated using both broth microdilution and disk diffusion techniques. T activity was usually twofold or greater than C activity for individual strains in both sample populations. The minimal inhibitory concentration (MIC) values of T and C were ≤ 0.4 to >400 (median, 25) and 0.8 to >400 (median, 50) $\mu\text{g/ml}$, respectively, for the random sample and 1.6 to >400 (median, 50) and 12.5 to >400 (median, 200) $\mu\text{g/ml}$, respectively, for the select sample. For predicting susceptibility (MIC, ≤ 50 μg of T and ≤ 100 μg of C per ml), 75- μg T and 100- μg C disks were equivalent in accuracy for the random sample (T/T = 92.6%, T/C = 92.0%, C/T = 91.7%, C/C = 89.8%). Regression-line analyses of zones of inhibition versus MIC values for the four combinations showed coefficients of correlation to be -0.81, -0.76, -0.77, and -0.75, respectively. With the sample selected as being resistant to C, T was better than C for predicting T susceptibility ($P < 0.05$), and T was equivalent to C for predicting C susceptibility (T/T = 84.3%, T/C = 81.0%, C/T = 73.6%, C/C = 80.4%). Coefficients of correlation were -0.70, -0.74, -0.55, and -0.61, respectively. T and C disks were, therefore, equivalent for determining T and C susceptibilities, but the T disk was more reliable for determining T susceptibility in a population skewed with C-resistant strains.

Although investigators recently reported that the in vitro actions of ticarcillin and carbenicillin on *Pseudomonas aeruginosa* were nearly identical (5), most previous reports have shown ticarcillin to be more active (1, 3, 7-11). Because of this difference in in vitro susceptibilities and a report (10) that the 100- μg carbenicillin disk was unreliable in predicting ticarcillin susceptibility for *P. aeruginosa* at any ticarcillin minimal inhibitory concentration (MIC) value greater than 25 $\mu\text{g/ml}$, it has been suggested that a separate ticarcillin disk is needed to determine the susceptibilities of *P. aeruginosa* to ticarcillin.

This study was undertaken to evaluate the relative susceptibilities of recent clinical isolates of *P. aeruginosa* to ticarcillin and carbenicillin and to determine the reliability of the disk diffusion test, using both ticarcillin and carbenicillin disks in distinguishing resistant from susceptible strains. A randomly selected population and a population which was selected to be resistant to carbenicillin, as determined by disk diffusion tests performed by 10 referring hospitals, were studied.

MATERIALS AND METHODS

Microorganisms. A total of 253 strains of *P. aeruginosa* were studied. Of these, 108 strains were randomly selected from clinical isolates at the Ohio State University Hospital and 145 strains were selected by 10 referring hospitals as carbenicillin resistant, as determined by the disk diffusion procedure. The 10 referring hospitals selected strains with zone diameters of inhibition of ≤ 13 mm using the 100- μg carbenicillin disk and then forwarded the strains to the Division of Infectious Diseases Laboratory at the Ohio State University Hospital.

Antibiotics. The ticarcillin and carbenicillin antibiotics used in MIC determinations were prepared by dissolving laboratory standard powders in sterile, distilled water and then diluting them to a concentration of 800 $\mu\text{g/ml}$. The drugs were stored for a maximum of 1 month at -20°C .

The disks used were the 75- μg ticarcillin and 100- μg carbenicillin disks, which were stored at 4°C until used. Both the laboratory standard powders and disks were supplied by Beecham Laboratories.

Susceptibility tests. The MIC values of ticarcillin and carbenicillin for *P. aeruginosa* were determined by a broth microdilution technique (4), using Trypticase soy broth (BBL), pH 7.3, final drug concentra-

tions ranging from 400 to 0.4 $\mu\text{g/ml}$, and inocula of 10^5 to 10^6 colony-forming units per ml.

The disk diffusion tests were performed at the same time as the MIC tests. The procedure used was the one described by Bauer et al (2), which was later modified (6).

The breakpoints used for determination of susceptible strains of *P. aeruginosa* for both the MIC and disk diffusion tests were based on manufacturers' recommendations. For ticarcillin, susceptibility was defined as an MIC value of ≤ 50 $\mu\text{g/ml}$ or a zone of inhibition of ≥ 15 mm. For carbenicillin, susceptibility was defined as an MIC value of ≤ 100 $\mu\text{g/ml}$ or a zone of inhibition of ≥ 17 mm.

Data analysis. For both drugs, the results of the disk diffusion tests and microdilution tests were used to calculate the least-squares lines of regression and the coefficients of correlation (r). The radii of the zones of inhibition were squared, and the MICs were assigned $\log_2$ values. These data were then entered into a Hewlett-Packard 9825A programmable calculator for determination of the regression lines and r values. The chi-square analysis of data method was used for determination of statistical significance.

RESULTS

Comparative plots of the ticarcillin and carbenicillin MIC values for each strain in the random and select samples and the assigned breakpoints for distinguishing susceptible from resistant strains are shown in Fig. 1 and 2, respectively. In the random sample, ticarcillin and carbenicillin MIC values were ≤ 0.4 to >400 (median, 25) and 0.8 to >400 (median, 50) $\mu\text{g/ml}$,

respectively. Ticarcillin activity was twofold or greater than carbenicillin for 96 (90%) of the 107 evaluable strains. Eight (7%) strains were resistant to both drugs; four (4%) strains were resistant only to ticarcillin; and four (4%) strains were resistant only to carbenicillin. In the select sample, ticarcillin and carbenicillin MIC values were 1.6 to >400 (median, 50) and 12.5 to >400 (median, 200) $\mu\text{g/ml}$, respectively. Ticarcillin activity was twofold or greater than carbenicillin for 96 (72%) of the 133 evaluable strains. A total of 62 (43%) strains were resistant to both drugs; 7 (5%) were resistant only to ticarcillin; and 21 (15%) were resistant only to carbenicillin.

Results of the regression-line analyses of *P. aeruginosa* susceptibility data for the disk diffusion and MIC studies are shown in Table 1. In the random sample, the correlation coefficients using the 75- μg ticarcillin and 100- μg carbenicillin disks were similar. In the select sample, the correlations for both ticarcillin and carbenicillin MIC values were better using the 75- μg ticarcillin disk.

The predictability of ticarcillin and carbenicillin activity against the 108 random and 145 select strains of *P. aeruginosa* by the disk diffusion test is shown in Table 2. In the random sample, percentage of predictability was good ($>89\%$) for both the 75- μg ticarcillin and 100- μg carbenicillin disks. The largest difference between both disks was only 2.8%. In the select sample, the 75- μg ticarcillin disk was statistically

FIG. 1. Comparative plot of the ticarcillin and carbenicillin MIC values for the 108 strains of *P. aeruginosa* in the random sample. The MIC breakpoints for susceptible and resistant categories are also shown (light lines). $Y = A + BX$ where Y is the $\log_2$ MIC value of ticarcillin, X is the $\log_2$ MIC value of carbenicillin, A is the y intercept, and B is the slope.

FIG. 2. Comparative plot of the ticarcillin and carbenicillin MIC values for 145 strains of *P. aeruginosa* in the select sample. The MIC breakpoints for susceptible and resistant categories are also shown (light lines). $Y = A + BX$ where Y is the $\log_2$ MIC value of ticarcillin, X is the $\log_2$ MIC value of carbenicillin, A is the y intercept, and B is the slope.

TABLE 1. Regression-line analyses of the random and select samples of *P. aeruginosa* for ticarcillin and carbenicillin

Sample	No. of strains tested	Antibiotic disk (μ g)	Antibiotic MIC	Correlation coefficient (r)	Slope	y Intercept ^a
Random	108	Ticarcillin, 75	Ticarcillin	-0.81	-0.020	8.97
		Ticarcillin, 75	Carbenicillin	-0.76	-0.016	9.70
		Carbenicillin, 100	Ticarcillin	-0.77	-0.023	8.42
		Carbenicillin, 100	Carbenicillin	-0.75	-0.019	9.29
Select	145	Ticarcillin, 75	Ticarcillin	-0.70	-0.032	9.20
		Ticarcillin, 75	Carbenicillin	-0.74	-0.029	10.07
		Carbenicillin, 100	Ticarcillin	-0.55	-0.032	8.30
		Carbenicillin, 100	Carbenicillin	-0.61	-0.031	9.41

^a Expressed in log₂ scale; 1 = 0.8 μ g/ml.

TABLE 2. Predictability of ticarcillin and carbenicillin activity against 108 random and 145 select strains of *P. aeruginosa*, using the disk diffusion test

Disk/MIC ^a	% Predictability	
	Random sample	Select sample
T/T	92.6	84.3
T/C	92.0	81.0
C/T	91.7	73.6
C/C	89.8	80.4

^a T, Ticarcillin; C, carbenicillin.

better than the 100- μ g carbenicillin disk for predicting ticarcillin susceptibility ($P < 0.05$), and the 75- μ g ticarcillin disk was similar to the 100- μ g carbenicillin disk for predicting carbenicillin susceptibility (81.0 versus 80.4%). Percentage of predictability of MIC values for both disks decreased in the select sample.

DISCUSSION

The MIC results in the random sample substantiate the previously published reports (1, 3, 7-11) that showed ticarcillin to be two- to four-fold more active than carbenicillin against *P. aeruginosa*. The nearly identical activities of both drugs against *P. aeruginosa* reported by Kalkani and Marketos (5) were observed in only about 9% of the strains in the random sample. The increased ticarcillin activity was also seen in the select sample skewed with carbenicillin-resistant strains of *P. aeruginosa*. However, 28% of the strains in the select sample showed nearly identical susceptibilities to both drugs. The r values for the regression-line equation correlating ticarcillin and carbenicillin MIC values in the random and select samples were 0.84 and 0.82, respectively, indicating that the MIC of either drug could be predicted with knowledge of the MIC of the other drug.

Correlation coefficients and predictability of ticarcillin and carbenicillin susceptibilities were

as good or better for both sample populations with the 75- μ g ticarcillin disk. It appears, therefore, that the 75- μ g ticarcillin disk could be used for all disk diffusion studies for determining both ticarcillin and carbenicillin susceptibilities of *P. aeruginosa*. However, a population of *P. aeruginosa* skewed with ticarcillin-resistant strains should first be evaluated.

It is noteworthy that in the select sample skewed with carbenicillin-resistant strains of *P. aeruginosa* only 57% of the strains were resistant to carbenicillin by MIC criteria, reflecting the fact that the MIC values were scattered around the breakpoint. Also, upon retesting each strain in our laboratory, only 69% of the strains determined to be carbenicillin resistant by the 10 referring hospitals were resistant by zone criteria, reflecting the lack of reproducibility of the disk diffusion test in the community.

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