Is There Complete Cross-Resistance of Gram-Negative Bacilli to Gentamicin and Tobramycin?

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Received for publication 8 June 1972

No cross-resistance between gentamicin and tobramycin was found among 19 recent clinical isolates representing four genera of gram-negative bacilli.

Tobramycin is a new antibiotic that shares many of the biological and chemical properties of gentamicin (3). In comparison with gentamicin in vitro, it has been shown to be more active against *Pseudomonas*, less active against *Serratia*, and equally active against other *Enterobacteriaceae* and staphylococci (4). The question of whether or not there is cross-resistance between these two drugs is unresolved. Brusch et al. (2) observed significant degrees of resistance to tobramycin among each of 13 strains of *Pseudomonas* and 27 strains of other gram-negative rods that were highly resistant to gentamicin. In contrast, Black and Griffith (1) noted five strains of *Pseudomonas* that were highly resistant to gentamicin, but susceptible to tobramycin. Data presented in this report suggest that cross-resistance is not complete among at least 19 clinical isolates from four genera of gram-negative bacilli.

The activities of gentamicin and tobramycin were assayed by the broth dilution method. Serial twofold dilutions of the drugs were made in brain heart infusion broth (Difco). Approximately 2×10^4 to 4×10^4 organisms were inoculated, and tubes were examined for turbidity after incubation for 18 hr at 37 C. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of drug that prevented visible growth. Organisms with an MIC of 6.25 or less $\mu\text{g/ml}$ were considered susceptible; those with a higher MIC were designated resistant. Only those differences in activity between the two drugs of fourfold or greater were considered significant.

Two hundred-thirty-five recent clinical isolates representing 10 genera were tested (*Escherichia*, 22; *Klebsiella*, 20; *Enterobacter*, 20; *Salmonella*, 20; *Shigella*, 20; *Citrobacter*, 18; *Acinetobacter*, 7; *Serratia*, 13; *Pseudomonas*, 20; *Proteus*, indole-positive, 54; and *Proteus*, indole-negative, 21). Of these, 37 (16%) were resistant to one or both drugs. Table 1 shows the MIC for these 37 strains. Among the 37, 18 were resistant to both drugs, 8 were resistant to gentamicin only, and 11 were resistant to tobramycin only.

There are few widely accepted definitions of microbial resistance for any single antimicrobial agent. Definitions must be based, in part, upon the agent under investigation, the method of assay for antimicrobial activity, and the medium used in the assay. Regardless of the definition, it is frequently difficult to extrapolate from in vitro results to in vivo activity. Yet, with all its limitations, this extrapolation must be attempted to facilitate the selection of antimicrobial therapy in practice.

For this study, organisms with an MIC of greater than 6.25 $\mu\text{g/ml}$ were considered resistant. Choice of this level for resistance was based on the practical considerations of concentrations achievable in human serum without significant risk of toxicity and of the accuracy of the assay method used (no greater than a twofold error). Organisms with an MIC of 12.5 $\mu\text{g/ml}$ were considered moderately resistant, and those with an MIC of greater than or equal to 25.0 $\mu\text{g/ml}$ were considered highly resistant.

TABLE 1. *Minimal inhibitory concentrations of gentamicin and tobramycin for resistant gram-negative bacilli*

Genus and strain	Minimal inhibitory concn ($\mu\text{g/ml}$)	
	Genta-mycin	Tobra-mycin
Strains resistant to both drugs		
<i>Escherichia</i> F21.....	50	25
<i>Escherichia</i> F78.....	25	12.5
<i>Acinetobacter</i> 1.....	>50	>50
<i>Acinetobacter</i> 3.....	>50	>50
<i>Acinetobacter</i> 4.....	>50	>50
<i>Proteus</i> (indole-negative) strain T.....	25	50
<i>Proteus</i> (indole-positive)		
Strain 133.....	25	25
Strain 34.....	12.5	25
Strain 43.....	50	>50
Strain 44.....	50	12.5
Strain 97.....	25	50
Strain 101.....	50	>50
Strain 104.....	25	25
Strain 106.....	25	>50
Strain 117.....	25	50
Strain 118.....	50	50
Strain 123.....	12.5	50
Strain 124.....	25	25
Strains resistant to one drug only		
<i>Enterobacter</i> 26.....	1.56	50
<i>Serratia</i> 7.....	1.56	12.5
<i>Serratia</i> 14.....	1.56	12.5
<i>Serratia</i> 17.....	1.56	12.5
<i>Acinetobacter</i> 2.....	1.56	50
<i>Proteus</i> (indole-negative)		
Strain 2.....	12.5	3.12
Strain 21.....	12.5	1.56
Strain 26.....	12.5	0.78
Strain 27.....	12.5	1.56
Strain 31.....	12.5	1.56
Strain 40.....	25	0.78
Strain 42.....	12.5	1.56
Strain 126.....	25	0.78
<i>Proteus</i> (indole-positive)		
Strain 100.....	3.12	25
Strain 125.....	3.12	25
Strain 89.....	3.12	50
Strain 96.....	3.12	12.5
Strain 122.....	3.12	50
Strain 36.....	6.25	25

Comparison of our results with those of Brusch et al. (2) reveals both similarities and differences. All of the strains reported by Brusch et al. (2) were highly resistant to gentamicin and were also resistant to tobramycin. In the present study, 16 of 18 strains highly resistant to gentamicin were also resistant to tobramycin; 2 were not. Of 23 strains highly resistant to tobramycin, 16 were also resistant to gentamicin; 7 were not. It is noteworthy that not all of the genera tested by Brusch et al. (2) were included in this study. This may account, in part, for the differences between the conclusions of the two studies.

In the present study, the greatest difference in susceptibility of organisms to these two drugs was found among those strains moderately resistant to one of the drugs. Four of 14 strains moderately resistant to one drug were also resistant to the other, whereas the remainder were resistant to one drug only.

The results of this study indicate that cross-resistance between gentamicin and tobramycin is not complete, regardless of definition of "resistance." However, the degree of cross-resistance observed does appear to increase as the degree of resistance to one of the two drugs increases.

Based upon studies to date, and assuming that tobramycin becomes available for clinical use, it would be erroneous to extrapolate results of an assay of the activity of only one agent to the other.

This investigation was supported by grants-in-aid from Eli Lilly & Co., Indianapolis, Ind., and Schering Corp., Bloomfield, N.J.

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