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Comparative Activity of Sisomicin, Gentamicin, Kanamycin, and Tobramycin

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Gentamicin, sisomicin, tobramycin, and kanamycin were compared in parallel tests in vitro and in vivo against a variety of bacterial strains and species. A number of differences were seen in vitro, in particular: (i) the lower activity of kanamycin, (ii) the greater activity of tobramycin against *Pseudomonas*, (iii) the greater activity of gentamicin and sisomicin against *Serratia*, and (iv) the generally similar results with tobramycin, gentamicin, and sisomicin against species other than *Pseudomonas* and *Serratia*, with the ranking in order of decreasing activity being sisomicin, gentamicin, and tobramycin. Analysis of disc test results suggested that the gentamicin disc is not adequate for testing the susceptibility of all bacteria to sisomicin or tobramycin. In vivo tests did not confirm all specifics of in vitro tests; results of in vivo tests indicated that sisomicin may be the most active. It is suggested that the place of each of the antibiotics in human therapy can best be evaluated by more rigorous in vivo tests and clinical studies rather than extensive in vitro comparisons.

The introduction of new, useful aminoglycoside antibiotics has progressed at a modest pace. Today, the most commonly used parenteral aminoglycoside antibiotics are kanamycin and gentamicin. Recently, two additional potentially useful parenteral aminoglycoside antibiotics have been described. These are tobramycin and sisomicin. Structures have been published for kanamycin (11), gentamicin (4), tobramycin (7), and sisomicin (3). Many published laboratory studies have compared gentamicin with kanamycin, and some have compared gentamicin with sisomicin (13) or gentamicin with tobramycin (5, 8–10, 12). Few studies, however, have involved a comparative evaluation of the four aminoglycoside antibiotics in parallel tests. Such a study is the subject of this report.

MATERIALS AND METHODS

Gentamicin, sisomicin, and kanamycin were used in the form of the sulfate, whereas tobramycin was used as the base; all values are corrected in terms of the base. Tobramycin was obtained from Eli Lilly & Co., and kanamycin was obtained from Bristol Laboratories. For reference purposes, carbenicillin (Beecham Inc.) and polymyxin B sulfate (Pfizer Inc.) were used. The strains of bacteria utilized in the study were from a variety of sources, but in all cases represent recent clinical isolates. Identification of all strains was confirmed by usual biochemical test procedures (2).

Disc tests. Disc susceptibility tests were done with commercially available 10-μg gentamicin discs and 30-μg kanamycin discs. The 10-μg sisomicin discs were prepared for use by BBL; 10-μg tobramycin discs were prepared in our laboratory. The disc test procedure used was identical to that conventionally known as the Bauer-Kirby procedure (1, 6). Mueller-Hinton agar (BBL) was used in plastic disposable petri dishes (Falcon Plastics).

Broth dilution tests. Broth dilution tests were done in Mueller-Hinton broth (BBL) in a volume of 3 ml/tube with an inoculum of approximately 5×10^4 to 1×10^5 organisms. This inoculum was obtained by appropriate dilution of an 18-hr broth culture (0.05 ml of a 1:1,000 dilution). For broth dilution tests, stock concentrations were freshly prepared in sterile distilled water and added to 100-ml quantities of broth to obtain twofold dilutions of antibiotic concentrations based on 1 μg/ml. These concentrations ranged from 0.03 to 256 μg/ml in terms of the base. Tubes were read visually after incubation for 18 to 24 hr at 37 C. Tests with *Mycoplasma* were done in PPLO broth with added serum and yeast extract; end points were determined by streaking on PPLO agar.

In vivo tests. Mouse protection tests were done in male CF-1 mice weighing approximately 20 g each, in treatment groups of seven each at five to seven dose levels with 10 untreated controls. Mice were treated with a single subcutaneous dose 1 hr after intraperitoneal infection with approximately 10^7 organisms/mouse. Controls generally died in 18 to 24 hr; protective dose 50% (PD_{50}) and protective dose 90% (PD_{90}) values were calculated by probit procedures based on mice surviving 48 hr after infection. In all

tests of a comparative nature, the antibiotics were run in parallel.

RESULTS

Broth dilution tests. The comparative in vitro activity of the various aminoglycoside antibiotics determined in broth dilution tests against gram-positive bacteria is shown in Table 1 in terms of cumulative percent susceptible to various concentrations of antibiotic. Similar results for *Pseudomonas* are shown in Table 2, for other gram-negative bacteria in Table 3, and for *Mycoplasma* in Table 4.

Gentamicin, sisomicin, and tobramycin had a similar high degree of activity against *Staphylococcus*, with gentamicin and sisomicin being slightly more active than tobramycin in terms of levels required to inhibit all strains (Table 1). Kanamycin was significantly less active against the *Staphylococcus* strains studied. The data for streptococci and enterococci (Table 1) show a graded degree of activity; sisomicin was the most active, followed by gentamicin, tobramycin, and kanamycin. However, none of the four approached the potency of penicillins and cephalosporins against *Streptococcus*.

The anti-*Pseudomonas* activity of the four aminoglycosides is shown in Table 2, with the strains separated into gentamicin-susceptible and gentamicin-resistant ones. Data for polymyxin B and carbenicillin have been included for reference purposes. Tobramycin was the most active of the aminoglycosides against *Pseudomonas* strains, and kanamycin had the least activity. Gentamicin was less active than tobramycin, and sisomicin fell between gentamicin and tobramycin. Tobramycin was slightly less active against gentamicin-resistant strains than against gentamicin-susceptible strains, owing in part to the use of some strains with resistance to both antibiotics. Sisomicin also showed a dramatic shift, being much more active against gentamicin-susceptible strains than against gentamicin-resistant strains. It was, however, substantially more effective than gentamicin against the resistant strains. Polymyxin B was highly active against all *Pseudomonas* strains, whereas carbenicillin had a potency only slightly better than that of kanamycin.

The data for *Escherichia coli* (Table 3) show gentamicin and tobramycin to have similar activity against the *E. coli* strains; sisomicin was slightly more active, and kanamycin was less active than the other three aminoglycosides. With *Klebsiella* strains (Table 3), sisomicin appeared more active against a higher number of strains than either gentamicin or tobramycin, with only small differences noted between gentamicin and tobramycin. As with the *E. coli* strains, *Klebsiella* strains were less susceptible to kanamycin than to the other three aminoglycosides.

Although the number of strains studied was small, *Serratia* strains (Table 3) showed a difference in susceptibility to the several aminoglycoside antibiotics. These strains were most highly susceptible to sisomicin and gentamicin, with lesser susceptibility to tobramycin and kanamycin. Sisomicin appeared to be more active than gentamicin with the small number of strains

TABLE 1. *Comparative in vitro activity of aminoglycosides against gram-positive bacteria*

Organism	Agent	Cumulative percent susceptible[a] to (μg/ml)								
		0.1	0.25	0.5	1	2	4	8	16	32
Staphylococcus aureus										
82 strains	Gentamicin	—	4	90	94	100				
43 strains	Sisomicin	—	4	63	98	100				
82 strains	Tobramycin	6	33	67	75	87	100			
43 strains	Kanamycin	—	—	21	60	63	70	91	96	100
Streptococcus pyogenes										
27 strains	Gentamicin	—	—	—	29	63	100			
27 strains	Sisomicin	—	—	—	33	100				
22 strains	Tobramycin	—	—	—	11	26	71	100		
27 strains	Kanamycin	—	—	—	—	26	26	100		
Enterococci										
15 strains	Gentamicin	—	—	—	7	13	100			
15 strains	Sisomicin	—	—	—	20	80	100			
15 strains	Tobramycin	—	—	—	7	7	33	100		
15 strains	Kanamycin	—	—	—	7	7	7	73	73	100

[a] Minimal inhibitory concentrations were determined in Mueller-Hinton broth.

TABLE 2. *Comparative in vitro activity of aminoglycosides, carbenicillin, and polymyxin B against Pseudomonas aeruginosa*

Pseudomonas strains	Agent	Cumulative percent susceptible[a] to (μg/ml)									
		0.1	0.25	0.5	1	2	4	8	16	32	64
Gentamicin-susceptible											
121 strains	Gentamicin	—	47	72	91	92	100				
81 strains	Sisomicin	32	47	50	99	100					
121 strains	Tobramycin	57	60	75	89	98	100				
43 strains	Kanamycin	—	—	—	—	5	5	7	23	49	95
Gentamicin-resistant[b]											
41 strains	Gentamicin	—	—	—	—	—	19	44	71	83	88
41 strains	Sisomicin	—	—	—	10	44	61	81	83	83	88
41 strains	Tobramycin	34	39	54	61	71	80	93	95	95	95
41 strains	Kanamycin	—	—	—	—	—	—	24	32	49	54
All strains											
162 strains	Gentamicin	—	37	55	69	70	81	89	94	98	99
122 strains	Sisomicin	22	32	34	71	84	90	96	98	98	99
162 strains	Tobramycin	52	55	71	84	88	94	99	99	99	99
84 strains	Kanamycin	—	—	—	—	2	2	16	27	49	76
42 strains	Polymyxin	40	100								
42 strains	Carbenicillin	—	—	—	—	2	12	31	48	74	76

[a] Minimal inhibitory concentrations were determined in Mueller-Hinton broth.

[b] Of the 41 strains, 18 were isolates from one burn unit and 15 were isolates from another burn unit; these may represent repeated isolates of the same strain. The other 8 strains were from a variety of sources; therefore the 41 strains tested may in fact represent as few as 10 different strains.

TABLE 3. *Comparative in vitro activity of aminoglycoside antibiotics against gram-negative bacteria*

Organism	Agent	Cumulative percent susceptible[a] to (μg/ml)								
		0.1	0.25	0.5	1	2	4	8	16	32
Escherichia coli, 52 strains	Gentamicin	—	2	22	62	72	94	98	100	
	Sisomicin	4	6	10	59	74	88	100		
	Tobramycin	—	—	4	74	79	91	94	98	100
	Kanamycin	—	—	0	13	63	83	94	98	100
Klebsiella pneumoniae, 71 strains	Gentamicin	3	25	42	66	73	79	96	99	100
	Sisomicin	17	25	27	66	80	96	100		
	Tobramycin	3	28	49	61	70	82	96	99	100
	Kanamycin	—	9	20	44	63	68	70	92	94
Indole-positive *Proteus*, 20 strains	Gentamicin	—	60	65	80	90	95	100		
	Sisomicin	—	65	80	90	95	100			
	Tobramycin	—	55	65	90	90	90	100		
	Kanamycin	—	—	15	50	70	85	95	95	100
Salmonella sp., 15 strains	Gentamicin	—	40	80	100					
	Sisomicin	—	40	93	100					
	Tobramycin	—	20	60	93	100				
	Kanamycin	—	—	—	—	53	87	100		
Serratia sp., 7 strains	Gentamicin	—	29	86	86	100				
	Sisomicin	—	57	100						
	Tobramycin	—	—	29	29	86	100			
	Kanamycin	—	—	—	14	57	86	86	86	86

[a] Minimal inhibitory concentrations were determined in Mueller-Hinton broth.

studied. With the indole-positive *Proteus* strains studied (Table 3), sisomicin was most active, followed by tobramycin and gentamicin; kanamycin was least active. A similar relationship was found with the 15 strains of *Salmonella* (Table 3), with the decreasing order of activity being sisomicin, gentamicin, tobramycin, and kanamycin.

The small number of *Mycoplasma* strains studied (Table 4) represent four of *M. pneumoniae*, five of *M. orale*, five of *M. salivarium*, and one of *M. hominis*. With these strains, sisomicin had the highest activity, followed by tobramycin, gentamicin, and kanamycin, in order of decreasing activity.

On the basis of the above cumulative broth dilution susceptibility data, marked differences among the drugs appeared only with *Pseudomonas* and *Serratia* strains. Against *Pseudomonas*, tobramycin was the most active, gentamicin was less so, and sisomicin was between these two. The *Serratia* strains were most susceptible to sisomicin and gentamicin, and were less susceptible to tobramycin and kanamycin. The other species examined showed only modest differences in susceptibility to the four aminoglycosides, except for kanamycin. In general, sisomicin was slightly more active, followed by gentamicin, tobramycin, and kanamycin.

Disc tests. The results of disc susceptibility tests performed by the Bauer-Kirby procedure are shown in Table 5. Kanamycin was not tested against *Pseudomonas* strains. The data are displayed in terms of the number of strains giving various zone diameters and the cumulative percentage of strains giving at least each specific zonal response. The similarities in distribution of zone sizes among the aminoglycosides are more striking than are the differences. The differences were essentially limited to *Pseudomonas*, for which tobramycin consistently gave larger zone sizes than either sisomicin or gentamicin, whereas *Klebsiella* and *Proteus* tended to give larger zones with sisomicin, gentamicin, and kanamycin.

TABLE 4. *Comparative in vitro activity of aminoglycosides against 15 strains of Mycoplasma*[a]

Agent	Cumulative percent susceptible[b] to (μg/ml)					
	0.1	0.25	0.5	1	2	4
Gentamicin	—	—	—	33	80	100
Sisomicin	—	—	13	53	100	
Tobramycin	—	—	—	40	100	
Kanamycin	—	—	—	7	40	100

[a] *M. pneumoniae*, four strains; *M. orale*, five strains; *M. salivarius*, five strains; *M. hominis*, one strain.

[b] Minimal inhibitory concentrations were determined in PPLO broth.

Interrelationship of disc tests. Recent regulatory decisions (6) have suggested the preference for a single disc serving for the evaluation of susceptibility of organisms to a group of antibiotics. With this in mind, we compared the zone sizes for gentamicin, sisomicin, and tobramycin for 334 strains (Table 6). Shown are the mean zone sizes against each group of pathogens. Correlation coefficients (R) were calculated showing the degree of association (from -1.0 to $+1.0$) for each pair (sisomicin-gentamicin, tobramycin-gentamicin), as were regression equations needed to estimate the sisomicin or tobramycin zonal response when the gentamicin disc was used. As an example, the correlation coefficient between gentamicin and sisomicin zone sizes for 43 strains of *S. aureus* was 0.91. The sisomicin zonal response for a *Staphylococcus* strain can be estimated by adding 3.93 to 0.85 times the gentamicin zone size. Correlation coefficients between gentamicin and sisomicin averaged 0.94 for all organisms and were higher than correlation coefficients between gentamicin and tobramycin. The latter was 0.58 for all organisms but was 0.87 when *Pseudomonas* was deleted. Low correlation coefficients were seen between gentamicin and sisomicin for enterococci and *Serratia* strains, whereas low values were seen between gentamicin and tobramycin for streptococci, enterococci, *Pseudomonas*, and *Serratia*. These findings suggest the need for individual susceptibility discs for each of these antibiotics.

In vivo activity. The comparative in vivo activity of the four aminoglycosides was studied in parallel protection tests in mice (Table 7). With all antibiotics, inspection of the ratios of PD_{50} to PD_{90} suggests that the slopes of responses are not the same. A general summarization of the data would suggest that sisomicin is the most highly active in vivo, followed by gentamicin, tobramycin, and kanamycin, although the differential activity between gentamicin and tobramycin is in many cases minimal. The striking in vitro difference in susceptibility of *Pseudomonas* strains to tobramycin, relative to gentamicin and sisomicin, was not demonstrated in vivo. In each instance, sisomicin was the most highly active, followed by tobramycin and gentamicin.

DISCUSSION

The studies reported above provide for a comparative evaluation of some aspects of the in

TABLE 5. *Distribution of zone diameters determined by the Bauer-Kirby procedure with standard susceptibility discs*[a]

Organism	Agent	Disc strength (μg)	Zone size (mm)								
			>30	27-29	24-26	21-23	18-20	15-17	12-14	9-11	<9
Pseudomonas aeruginosa											
84 strains	Gentamicin	10	1 (1)	9 (12)	24 (41)	10 (52)	3 (56)	4 (61)	8 (70)	9 (81)	16 (100)
104 strains	Sisomicin	10	1 (1)	17 (17)	28 (44)	9 (53)	5 (58)	11 (68)	16 (86)	8 (93)	7 (100)
84 strains	Tobramycin	10	5 (6)	26 (37)	28 (70)	6 (77)	6 (85)	5 (90)	2 (93)	2 (95)	4 (100)
Klebsiella pneumoniae											
71 strains	Gentamicin	10	0	0	20 (28)	27 (66)	6 (75)	6 (83)	10 (97)	2 (100)	
82 strains	Sisomicin	10	2 (2)	2 (5)	22 (32)	28 (66)	9 (77)	7 (85)	10 (98)	2 (100)	
71 strains	Tobramycin	10	0	0	2 (3)	33 (49)	14 (69)	4 (75)	11 (90)	7 (100)	
71 strains	Kanamycin	30	0	2 (3)	27 (41)	25 (76)	3 (80)	3 (85)	1 (86)	1 (87)	9 (100)
Escherichia coli											
52 strains	Gentamicin	10	0	0	11 (21)	28 (75)	9 (92)	2 (95)	2 (100)		
64 strains	Sisomicin	10	0	0	14 (22)	39 (83)	9 (97)	0 (97)	2 (100)		
52 strains	Tobramycin	10	0	0	11 (21)	26 (71)	10 (90)	1 (92)	1 (94)	1 (96)	2 (100)
52 strains	Kanamycin	30	0	1 (2)	17 (35)	25 (83)	3 (89)	1 (90)	3 (96)	1 (98)	1 (100)
Staphylococcus aureus											
43 strains	Gentamicin	10	0	10 (23)	25 (81)	7 (98)	0 (98)	0 (98)	1 (100)		
53 strains	Sisomicin	10	2 (2)	10 (23)	30 (79)	8 (95)	1 (97)	2 (100)			
43 strains	Tobramycin	10	1 (2)	13 (33)	27 (96)	1 (98)	0 (98)	0 (98)	0 (98)	1 (100)	
43 strains	Kanamycin	30	0	14 (33)	20 (78)	4 (86)	0 (86)	0 (86)	1 (89)	3 (98)	1 (100)
Proteus											
26 strains	Gentamicin	10	0	0	8 (31)	14 (85)	4 (100)				
48 strains	Sisomicin	10	0	0	17 (35)	25 (87)	3 (94)	2 (98)	1 (100)		
26 strains	Tobramycin	10	0	0	1 (4)	17 (69)	5 (88)	3 (100)			
26 strains	Kanamycin	30	0	4 (15)	17 (81)	5 (100)					
Streptococcus pyogenes											
24 strains	Gentamicin	10	—	—	—	—	3 (12)	17 (83)	4 (100)		
36 strains	Sisomicin	10	—	—	—	3 (12)	10 (33)	14 (75)	9 (100)		
24 strains	Tobramycin	10	—	—	—	—	—	4 (16)	4 (33)	16 (100)	
24 strains	Kanamycin	30	—	—	—	—	—	1 (4)	5 (25)	9 (63)	9 (100)
Enterococci											
15 strains	Gentamicin	10	—	—	—	—	—	7 (47)	8 (100)		
25 strains	Sisomicin	10	—	—	—	1 (4)	4 (20)	6 (44)	13 (96)	1 (100)	
15 strains	Tobramycin	10	—	1 (7)				2 (20)	2 (33)	9 (93)	1 (100)
15 strains	Kanamycin	30	—	—	—	—	1 (7)	4 (33)	4 (47)	4 (73)	4 (100)

[a] Number of strains susceptible, with the cumulative percentage given in parentheses.

vitro and in vivo activity of two established aminoglycosides, gentamicin and kanamycin, and two new aminoglycosides, tobramycin and sisomicin. In broth dilution tests, gentamicin and sisomicin appear to be more active than tobramycin or kanamycin against gram-positive bacteria, with the exception of a group of *Staphylococcus* strains with greater susceptibility to tobramycin and reduced susceptibility to kanamycin. Broth dilution tests with *Pseudomonas* demonstrated more striking differences: tobramycin was the most active and kanamycin was least active; sisomicin and gentamicin followed tobramycin in that order. Tobramycin was slightly less active against gentamicin-resistant strains than against susceptible ones. Sisomicin was more active than gentamicin against gentamicin-resistant strains but was not as active as tobramycin. With the other gram-negative bacteria studied, differences between sisomicin, tobramycin, and gentamicin were small, although there were suggestions that the ranking, from most active to least active, might be sisomicin, gentamicin, and tobramycin, with kanamycin being less active.

Serratia strains showed a difference in susceptibility, being more highly susceptible to sisomicin and gentamicin than to tobramycin and kanamycin. Tests against *Mycoplasma* suggest that sisomicin may be slightly more active and kanamycin less active.

These in vitro test results are in general similar to those reported by others with regard to gentamicin and tobramycin (5, 9, 10, 12).

Examination of the zonal responses of a variety of strains to standard discs by the Bauer-Kirby procedure revealed only minor differences in re-

TABLE 6. *Interrelationship of disc test results with the Bauer-Kirby method*

Organism	No. of strains	Mean zone size (mm)			Correlation with gentamicin			
					Sisomicin		Tobramycin	
		Gentamicin, 10 μg	Sisomicin, 10 μg	Tobramycin 10 μg	R[a]	Estimating equation[b] ($\alpha + \beta$)	R[a]	Estimating equation[b] ($\alpha + \beta$)
Staphylococcus aureus	43	24.9	25.1	25.6	0.91	3.93 + 0.85 G	0.91	1.05 + 0.99 G
Streptococcus pyogenes	23	15.7	15.3	11.2	0.82	1.95 + 0.84 G	0.40	2.30 + 0.56 G
Enterococcus	15	14.7	14.1	11.3	0.65	0.02 + 0.96 G	0.65	−22.4 + 2.28 G
Escherichia coli	52	21.6	21.8	20.9	0.89	4.87 + 0.78 G	0.80	−4.16 + 1.16 G
Klebsiella sp.	69	20.4	20.4	18.6	0.96	1.95 + 0.90 G	0.89	0.99 + 0.86 G
Proteus	26	22.6	22.8	20.7	0.88	3.24 + 0.86 G	0.86	−1.00 + 0.95 G
Pseudomonas	84	17.9	19.9	23.9	0.94	5.31 + 0.81 G	0.59	16.38 + 0.42 G
Salmonella	15	24.8	25.0	21.3	0.91	3.08 + 0.88 G	0.81	4.27 + 0.69 G
Serratia	7	25.0	23.3	17.6	0.54	−14.21 + 1.50 G	0.41	−7.43 + 1.00 G
All except *Pseudomonas*	250	21.3	21.2	19.5	0.96	0.72 + 0.96 G	0.87	−4.33 + 1.12 G
All	334	20.46	20.92	20.60	0.94	3.5 + 0.85 G	0.58	8.23 + 0.61 G

[a] R = correlation coefficient.

[b] Estimating equation = factors given are *a* and *b* where the estimated zone size for sisomicin or tobramycin = $\alpha + \beta$ (gentamicin zone).

TABLE 7. *Comparative in vivo activity of aminoglycosides (protection tests in mice)*[a]

Infecting organism	Gentamicin		Sisomicin		Tobramycin		Kanamycin	
	PD_{50}	PD_{90}	PD_{50}	PD_{90}	PD_{50}	PD_{90}	PD_{50}	PD_{90}
Staphylococcus Gray	3.0	6.2	1.8	4.0	4.7	7.0	18.0	28.0
Staphylococcus 979	3.5	7.0	0.5	3.0	2.9	6.2	28.0	>50.0
Staphylococcus 306	0.5	5.7	0.3	0.6	0.5	6.3	5.0	14.2
Staphylococcus 16	7.2	11.2	2.8	3.4	6.4	10.5	24.0	31.0
Staphylococcus 226	2.6	5.7	1.5	4.1	3.5	7.0	11.5	29.5
Streptococcus pyogenes C	30.0	48.0	15.0	47.5	24.0	50.0	42.0	>50.0
Escherichia coli 7112	0.8	3.0	0.4	2.9	1.5	7.1	17.0	37.5
E. coli 279	25.0	54.0	19.0	33.0	15.0	>55.0	—	—
E. coli 11775	1.2	2.7	0.4	3.1	4.1	28.0	—	—
E. coli 887	8.4	30.0	6.3	32.0	27.0	52.0	—	—
E. coli 777	10.1	33.0	2.4	22.0	12.0	29.0	—	—
Klebsiella pneumoniae 680	0.4	2.9	0.4	0.7	0.5	2.6	15.0	>50.0
K. pneumoniae 63	0.6	3.2	0.3	0.6	0.4	2.7	—	—
K. pneumoniae 62	0.12	0.3	0.07	0.3	0.14	0.3	—	—
K. pneumoniae 60	0.07	0.11	0.07	0.11	0.05	0.3	—	—
K. pneumoniae 70	0.6	2.7	0.4	2.1	0.4	2.7	—	—
K. pneumoniae 75	0.3	2.9	0.2	2.1	0.4	2.8	—	—
Proteus sp. Gill	2.3	5.8	1.8	2.9	1.6	3.0	—	—
Pseudomonas aeruginosa 6841	0.5	7.1	0.4	3.1	2.0	5.7	12.8	>50.0
P. aeruginosa 416	11.5	15.0	3.2	5.8	3.9	5.9	>50.0	>50.0
P. aeruginosa 413	19.0	29.0	6.2	10.0	7.8	14.0	>50.0	>50.0
P. aeruginosa 464	1.2	3.1	0.3	0.6	0.4	0.5	—	—
P. aeruginosa 418	11.2	35.0	4.5	9.6	6.1	10.2	—	—
P. aeruginosa 205	3.5	7.1	2.8	6.1	3.1	6.7	—	—
Salmonella paratyphi B	3.2	5.7	1.8	4.5	8.0	9.3	31.0	>50.0
Salmonella sp. cubana I	4.4	8.1	1.1	3.1	12.0	31.0	—	—
S. typhimurium	7.8	31.0	6.0	28.0	22.0	>55.0	—	—
Salmonella Oslo	0.3	0.7	0.2	0.6	0.2	0.6	—	—

[a] The PD_{50} and PD_{90} are expressed in milligrams per kilogram.

sponse. *Pseudomonas* strains tended to give larger zones with tobramcyin discs, whereas *Klebsiella* and *Proteus* strains tended to give larger zones with sisomicin, gentamicin, and kanamycin discs.

It is clear from the analysis of the zonal response of a number of strains that separate discs will be required for each of the antibiotics, at least with regard to the Bauer-Kirby susceptibility method.

In vivo tests did not support all of the differences seen with in vitro tests, although the number of strains studied was small. Sisomicin was clearly the most active in vivo, even against *Pseudomonas* strains. These in vivo differences may well reflect absorption differences.

With specific attention to the overall comparative activity of the four aminoglycosides studied, in vitro tests would lead to the conclusion that tobramycin is most active against *Pseudomonas* and that sisomicin and gentamicin are most active against *Serratia*. Against all other species, differences are minimal, although sisomicin and gentamicin may be slightly more active than tobramycin. Kanamycin is less active than the other aminoglycosides. Except for the reduced activity of kanamycin, the above in vitro suggestions were not confirmed by in vivo testing. In vivo, sisomicin was most active against all species, and gentamicin and tobramycin had generally similar activity, except against less susceptible *Pseudomonas* strains.

This stresses the importance of other factors, such as absorption and excretion kinetics, as well as the various details of the nature of the infection (location, multiplication, host effects, etc.) in the experimental evaluation of antibiotics. It suggests that each of the aminoglycosides may have a place in the therapy of bacterial infections which can only be defined by more detailed in vivo and clinical studies.

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