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Comparison of the Antibacterial Activities of Sisomicin and Gentamicin Against Gram-Negative Bacteria

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Sisomicin was found to be more active on a weight basis than gentamicin against *Pseudomonas* sp., *Klebsiella* sp., and indole-positive *Proteus*. Gentamicin was more active than sisomicin against *Escherichia coli, Serratia* sp., *Enterobacter* sp., and *Proteus mirabilis*. Both antibiotics were very active against methicillin-resistant strains of *Staphylococcus aureus*.

Several reports have shown that sisomicin, a new aminoglycoside antibiotic, has a spectrum of activity in vitro similar to that of gentamicin, with increased activity against strains of *Pseudomonas aeruginosa* (2, 3, 5, 6). We report results comparing the antibacterial activities of sisomicin and gentamicin in vitro against clinical isolates in a large general hospital.

Minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) of sisomicin and gentamicin for the bacterial isolates were determined by the standard twofold tube-dilution method. As inoculum, 0.5 ml of a 10^{-4} dilution of overnight bacterial growth in Mueller-Hinton broth was used. Disk susceptibility tests on Mueller-Hinton agar were determined by the method of Bauer et al. (1). The effect of inoculum size on the MIC of sisomicin for four strains of *P. aeruginosa* and six strains of *Escherichia coli* was determined by inoculating 100-fold dilutions of the overnight growth of the organisms. Colony-forming units were determined by colony counting with the standard pour-plate method. The effect of human serum was determined by comparing the MICs and MBCs of sisomicin and gentamicin in Mueller-Hinton broth and 50% serum for five strains of *P. aeruginosa*.

Sisomicin was found to be highly active in vitro against most strains of *Pseudomonas* sp., *Klebsiella* sp., *Enterobacter* sp., *E. coli, Proteus* sp., and *Serratia* sp. tested (Table 1). *Pseudomonas* sp. were very susceptible to this compound; 96% of all strains tested were inhibited by a concentration of 0.4 μg/ml, compared to 0.8 μg of gentamicin per ml; the average MIC of sisomicin was 0.23 μg/ml, compared to 0.61 μg of gentamicin per ml (Table 1). The average MBC of sisomicin was 0.44 μg/ml, compared to 0.93% μg of gentamicin per ml. Agar-diffusion studies in Mueller-Hinton agar revealed an average zone size of 26.5 mm with sisomicin, compared to 24 mm with gentamicin. All strains of *Klebsiella* sp. tested were inhibited by sisomicin at a concentration of 0.75 μg/ml; for *E. coli* strains, MIC was 1.5 μg/ml. Gentamicin was slightly more active against *Proteus mirabilis* with an average MIC of 0.57 μg/ml, compared to 0.78 μg/ml for sisomicin. The MICs of sisomicin and gentamicin for strains of indole-positive *Proteus* sp. were 0.83 and 1.12 μmg/ml, respectively (Table 1). Sisomicin was highly active against most strains of *Enterobacter* sp. tested; 90% of strains were inhibited by 0.75 μg/ml. *Serratia* sp. were less susceptible to sisomicin than to gentamicin; 91% of strains were inhibited at 1.5 μg of sisomicin per ml, and 87% were inhibited at 0.75 μg of gentamicin per ml. Both sisomicin and gentamicin were very active against 10 strains of methicillin-resistant *Staphylococcus aureus* tested (Table 1).

When the inoculum size of both *P. aeruginosa* and *E. coli* was increased by 4 logs, up to an eightfold increase in MICs of both antibiotics was observed; greater effects on the MBCs were seen with larger inocula. The antibiotic concentrations needed for inhibition of *P. aeruginosa* were markedly higher in Trypticase soy broth than in Mueller-Hinton broth (Table 2). Human serum, at 50% concentration, increased the MIC of sisomicin eightfold against strains of *P. aeruginosa* (Table 3); the effect was less marked with gentamicin.

Sisomicin was bactericidal for most strains tested; in many instances the MBC approximated the MIC or revealed a twofold to fourfold difference. The average MICs of sisomicin for susceptible bacteria were well below the average peak serum level of 2.5 μg/ml obtained after an intramuscular dose of 20 mg/m² (4). Our data revealed sisomicin to be more active than gentamicin against *Pseudomonas* and

TABLE 1. *Comparison of in vitro antibacterial activity of sisomicin (S) and gentamicin (G)*

Microorganism	No. of strains	MIC (μg/ml)		MBC (μg/ml)		Kirby-Bauer method (zone size, mm)	
		S	G	S	G	S	G
Pseudomonas sp.	26	0.23 ± 0.14[a] (0.085–0.753)[b]	0.61 ± 0.27 (0.19–1.55)	0.44 ± 0.3 (0.085–1.56)	0.93 ± 0.39 (0.37–1.5)	26.5 ± 5.7 (20–32)	23.8 ± 7.1 (8–34)
Escherichia coli	24	0.59 ± 0.4 (0.085–1.5)	0.37 ± 0.24 (0.085–0.75)	1.26 ± 1.39 (0.085–6.7)	0.68 ± 0.8 (0.08–3)	23.1 ± 1.4 (21–26)	23.8 ± 1.6 (21–29)
Klebsiella sp.	21	0.44 ± 0.21 (0.175–0.75)	0.5 ± 0.24 (0.085–0.75)	0.52 ± 0.21 (0.175–0.75)	0.94 ± 0.78 (0.085–3)	22.1 ± .63 (20–23)	20.5 ± 1.5 (18–23)
Enterobacter sp.	21	0.59 ± 0.3 (0.17–1.5)	0.46 ± 0.38 (0.17–1.5)	0.64 ± 0.28 (0.17–1.5)	0.72 ± 0.64 (0.17–3.0)	22.2 ± 1.5 (20–26)	21.8 ± 1.53 (20–25)
Proteus mirabilis	24	0.78 ± 0.64 (0.04–3.12)	0.57 ± 0.43 (0.04–1.5)	0.9 ± 0.63 (0.04–3.12)	0.62 ± 0.46 (0.04–1.5)	25.1 ± 1.7 (22–31)	24.8 ± 1.8 (22–29)
Proteus sp. (indole positive)	9	0.83 ± 0.52 (0.38–1.5)	1.12 ± 0.45 (0.38–1.5)	1.25 ± 0.75 (0.75–3)	1.25 ± 0.37 (0.75–1.5)	24.66 ± 2.8 (19–29)	24.5 ± 2.9 (19–29)
Serratia sp.	22	1.0 ± 0.81 (0.17–3.15)	0.59 ± 0.42 (0.17–1.5)	3.47 ± 3.07 (0.35–12.5)	1.55 ± 1.15 (0.35–3.12)	23.2 ± 4.99 (21–28)	24.7 ± 1.12 (22–26)
Staphylococcus aureus (methicillin resistant)	10	0.78 ± 0.45[c] (0.39–1.56)	1.2 ± 0.85[c] (0.39–3.13)	1.83 ± 0.95[c] (0.39–3.13)	1.95 ± 1.05[c] (0.78–3.13)		

[a] Mean ± standard deviation.
[b] Range.
[c] Determined after 48 h of incubation.

TABLE 2. *Effects of different media on the MICs (μg/ml) of sisomicin (S) and gentamicin (G) against P. aeruginosa*

Strain		MIC	
		Mueller-Hinton broth	Trypticase soy broth
794	S	0.19	5
	G	0.75	5
362	S	0.37	5
	G	0.75	>5
754	S	0.19	5
	G	0.37	5
005	S	0.37	2.5
	G	0.75	5
717	S	0.19	5
	G	0.37	

TABLE 3. *Effects of 50% serum on the MICs and MBCs (μg/ml) of sisomicin (S) and gentamicin (G) against P. aeruginosa*

Strain		MIC		MBC	
		Broth	Serum	Broth	Serum
815	S	0.4	3.12	1.6	3.12
	G	0.8	3.12	0.8	3.12
887	S	0.37	3.12	3.12	3.12
	G	0.37	3.12	3.12	3.12
656	S	0.37	3.12	1.6	3.12
	G	0.37	1.5	1.6	1.5

Klebsiella strains, in agreement with previous reports (2, 3, 5, 6). However, in contrast to our results, Young and Hewitt (6) found sisomicin to have greater activity than gentamicin against *Enterobacter* sp. In agreement with others (3, 5, 6), we found *Serratia* strains to be less susceptible to sisomicin than gentamicin. Clinical studies will be required to determine whether sisomicin will have any therapeutic advantage over gentamicin.

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