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Antimicrobial Activity In Vitro of Netilmicin and Comparison with Sisomicin, Gentamicin, and Tobramycin

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The antimicrobial activity of netilmicin, a new semisynthetic aminoglycosidic aminocyclitol, was determined against 123 recent gram-negative clinical isolates susceptible to gentamicin and 60 isolates resistant to either sisomicin, gentamicin, or tobramycin. The minimal inhibitory concentrations and minimal bactericidal concentrations of netilmicin, sisomicin, gentamicin, and tobramycin against *Pseudomonas*, *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Proteus mirabilis*, and indole-positive *Proteus* were, in general, quite similar. Gentamicin was the most active against *Serratia*. A total of 54, 67, and 88% of gentamicin-resistant *Pseudomonas*, *Serratia*, and *Klebsiella*, respectively, were susceptible to netilmicin. Strains of indole-positive *Proteus*, *Acinetobacter*, *Providencia*, and *E. coli* resistant to gentamicin were likely to be resistant also to netilmicin.

Netilmicin (Sch 20569) is a new semisynthetic aminoglycosidic aminocyclitol antibiotic similar both in structure and spectrum of antimicrobial activity to gentamicin and sisomicin. Initial work has suggested that netilmicin may be effective against gentamicin-resistant strains of gram-negative bacteria (3) and may have less oto- and nephrotoxicity than gentamicin (Informational material for investigational drug Sch 20569, Schering Corp., Bloomfield, N.J., 1975). We report results of the comparison of the antimicrobial activity in vitro of netilmicin, sisomicin, gentamicin, and tobramycin against recent clinical gram-negative isolates.

MATERIALS AND METHODS

Gram-negative bacterial isolates from recent clinical specimens were obtained from the diagnostic microbiology laboratory of The Mount Sinai Hospital. The isolates included 123 strains susceptible to gentamicin and 60 strains resistant to either gentamicin, sisomicin, or tobramycin. The gentamicin-susceptible strains included 20 *Pseudomonas* sp., 21 *Escherichia coli*, 24 *Klebsiella* sp., 22 *Enterobacter* sp., 9 *Proteus mirabilis*, 9 *Proteus* sp. (indole positive), and 18 *Serratia* sp. The gentamicin-resistant isolates included 13 *Pseudomonas* sp., 2 *Enterobacter* sp., 17 *Klebsiella* sp., 4 indole-positive *Proteus* sp., 13 *Serratia* sp., 2 *Providencia* sp., 6 *E. coli*, and 3 *Acinetobacter* sp. Minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) of netilmicin, sisomicin, gentamicin, and tobramycin for the isolates were determined by the standard twofold tube dilution method in Mueller-Hinton broth as previously described (1, 2). Bacterial isolates inhibited by concentrations ≥6.25 μg/ml of the aminoglycosides were considered to be resistant strains. Netilmicin, sisomicin, and gentamicin were obtained from Schering Corp., Bloomfield, N.J., and tobramycin was obtained from Eli Lilly and Co., Indianapolis, Ind.

RESULTS

The antimicrobial activity in vitro of netilmicin overall was comparable to that of sisomicin, gentamicin, and tobramycin against 123 gram-negative isolates susceptible to gentamicin (Table 1). Neticilin (mean MIC, 0.95 μg/ml) was slightly less active than gentamicin (mean MIC, 0.73 μg/ml) against the 20 strains of gentamicin-susceptible *Pseudomonas* sp. tested; 71% of strains of *Pseudomonas* were inhibited at a concentration of netilmicin of 0.78 μg/ml, whereas 81% were inhibited at the same concentration of gentamicin. Both sisomicin (mean MIC, 0.37 μg/ml) and tobramycin (mean MIC, 0.39 μg/ml) were much more active against these strains. The MICs were only slightly lower than the MBCs.

The mean MIC of netilmicin for 21 strains of *E. coli* tested (0.75 μg/ml) was slightly higher than the mean MIC of gentamicin (0.63 μg/ml), but was lower than the mean MICs of sisomicin (0.85 μg/ml) and tobramycin (0.93 μg/ml) for these strains (Table 1). Eighty-one percent of *E. coli* tested were inhibited by a concentration of 0.78 μg of netilmicin or sisomicin per ml; 90% were inhibited at the same concentration of gentamicin. The mean MICs of the four aminoglycosides were similar against 24 strains of *Klebsiella* sp. tested. Eighty-three percent of *Klebsiella* were inhibited at a concentration of

TABLE 1. *Comparison of in vitro antibacterial activity of netilmicin (N), sisomicin (S), gentamicin (G), and tobramycin (T)*

Microorganism	No. of strains	MIC (μg/ml)				MBC (μg/ml)			
		N	S	G	T	N	S	G	T
Pseudomonas sp.	20	0.95 ± 0.65[a] (0.39 – 3.12)[b]	0.37 ± 0.16 (0.2 – 0.78)	0.73 ± 0.40 (0.2 – 1.56)	0.39 ± 0.18 (0.2 – 0.78)	1.79 ± 1.45 (0.39 – 6.25)	0.62 ± 0.65 (0.2 – 3.12)	1.18 ± 0.82 (0.2 – 3.12)	0.66 ± 0.61 (0.2 – 3.12)
Escherichia coli	21	0.75 ± 0.44 (0.2 – 1.56)	0.85 ± 0.38 (0.39 – 1.56)	0.63 ± 0.37 (0.2 – 1.56)	0.93 ± 0.67 (0.2 – 3.12)	1.19 ± 1.32 (0.2 – 6.25)	1.02 ± 0.62 (0.39 – 3.12)	0.97 ± 0.65 (0.2 – 3.12)	1.44 ± 0.92 (0.9 – 3.12)
Klebsiella sp.	24	0.41 ± 0.20 (0.2 – 0.78)	0.41 ± 0.18 (0.2 – 0.78)	0.45 ± 0.2 (0.2 – 0.78)	0.5 ± 0.22 (0.2 – 0.78)	0.67 ± 0.62 (0.2 – 3.12)	0.58 ± 0.37 (0.2 – 1.56)	0.54 ± 0.36 (0.2 – 1.56)	0.56 ± 0.31 (0.2 – 0.78)
Enterobacter sp.	22	0.76 ± 0.59 (0.39 – 3.12)	0.67 ± 0.58 (0.2 – 3.12)	0.61 ± 0.59 (0.2 – 3.12)	0.78 ± 0.58 (0.39 – 3.12)	1.04 ± 0.90 (0.39 – 3.12)	0.83 ± 0.79 (0.2 – 3.12)	0.75 ± 0.79 (0.2 – 3.12)	0.9 ± 0.6 (0.39 – 3.12)
Proteus mirabilis	9	0.95 ± 0.48 (0.39 – 1.56)	0.98 ± 0.56 (0.39 – 1.56)	0.56 ± 0.26 (0.2 – 0.78)	0.67 ± 0.40 (0.2 – 0.78)	1.39 ± 0.78 (0.78 – 3.12)	0.99 ± 0.55 (0.39 – 1.56)	0.87 ± 0.90 (0.02 – 0.78)	1.3 ± 1.09 (0.2 – 3.12)
Proteus sp. (indole positive)	9	0.56 ± 0.20 (0.39 – 0.78)	0.65 ± 0.19 (0.39 – 0.78)	0.60 ± 0.39 (0.39 – 1.56)	0.73 ± 0.36 (0.39 – 1.56)	1.25 ± 1.11 (0.39 – 3.12)	1.35 ± 1.06 (0.39 – 3.12)	1.12 ± 0.85 (0.39 – 3.12)	1.4 ± 0.72 (0.78 – 3.12)
Serratia sp.	18	2.73 ± 0.77 (0.78 – 3.12)	1.69 ± 0.72 (0.78 – 3.12)	1.25 ± 0.79 (0.39 – 3.12)	3.91 ± 2.10 (1.56 – 6.25)	3.29 ± 1.5 (1.56 – 6.25)	1.82 ± 0.75 (0.78 – 3.12)	1.47 ± 0.87 (0.78 – 3.12)	4.76 ± 2.53 (1.56 – 12.5)

[a] Mean ± standard deviation.
[b] Range.

0.39 μg of netilmicin or sisomicin per ml, whereas 75 and 63% were inhibited at the same concentration of gentamicin and tobramycin, respectively. Gentamicin and sisomicin were slightly more active against *Enterobacter* than netilmicin and tobramycin; 95% of strains of *Enterobacter* tested were inhibited by 1.56 μg of netilmicin, sisomicin, gentamicin, and tobramycin per ml. Gentamicin and tobramycin were more active against the strains of *P. mirabilis* tested than were netilmicin and sisomicin. The activities of netilmicin, sisomicin, and gentamicin against nine strains of indole-positive *Proteus* were equivalent. Gentamicin and sisomicin were more active against the 18 strains of *Serratia* tested than were netilmicin and tobramycin. Netilmicin was slightly more active than tobramycin against these strains. Ninety percent of the strains of *Serratia* were inhibited at a concentration of gentamicin of 1.56 μg/ml, whereas 24% of the strains were inhibited at the same concentration of netilmicin; 81% were inhibited by a concentration of 1.56 μg of sisomicin per ml, but only 5% were inhibited at the same concentration of tobramycin.

The antimicorbial activity of netilmicin against 60 gram-negative isolates resistant to either sisomicin, gentamicin, or tobramycin is presented in Fig. 1 and Table 2. Fifty-four percent of gentamicin-resistant strains of *Pseudomonas* were susceptible to netilmicin; 38% of the strains were susceptible to tobramycin, but all were resistant to sisomicin (Fig. 1). Sixty-seven percent of gentamicin-resistant *Serratia* were susceptible to netilmicin (Fig. 1). All the gentamicin-resistant strains of *Serratia* were resistant to sisomicin, whereas 33% were susceptible to tobramycin. Eighty-eight percent of gentamicin-resistant *Klebsiella* were susceptible to netilmicin; all the strains were resistant to sisomicin, whereas only 12% were susceptible to tobramycin (Fig. 1). The two isolates of gentamicin-resistant *Enterobacter* tested were susceptible to netilmicin (Table 2). However, all the gentamicin-resistant strains of indole-positive *Proteus, Acinetobacter, Providencia,* and *E. coli* were resistant also to netilmicin (Table 2).

DISCUSSION

Our results confirm the data presented recently by Rahal et al. (3) indicating that netilmicin may be an effective antimicrobial agent against gram-negative bacteria and may be especially useful for treatment of infections caused by gentamicin-resistant *Enterobacteriaceae*. All gentamicin-resistant *E. coli* and *Klebsiella* tested by Rahal et al. (3) were susceptible

to netilmicin, but these authors did not find netilmicin to be useful against gentamicin-resistant *Pseudomonas*. In contrast, 54% of gentamicin-resistant strains of *Pseudomonas* we tested were susceptible to netilmicin, whereas all our gentamicin-resistant strains of *E. coli* were resistant also to netilmicin. Netilmicin was active against gentamicin-resistant strains of *Serratia, Klebsiella,* and *Enterobacter*. However, gentamicin-resistant strains of indole-positive *Proteus, Acinetobacter,* and *Providencia* appear likely to be resistant also to netilmicin.

Chronic toxicity studies in the rat, dog, and cat suggest that netilmicin may have significantly less oto- and nephrotoxicity than gentamicin. In contrast, acute toxicity studies in these animals revealed netilmicin to have greater toxicity than gentamicin, perhaps due to greater neuromuscular blockade by netilmicin at the higher dose levels. Blood levels of netilmicin in animals are equivalent to those of gentamicin when similar doses are administered (Informational material for the investigational drug Sch 20569, Schering Corp., Bloomfield, N.J., 1975). The effectiveness of netilmi-

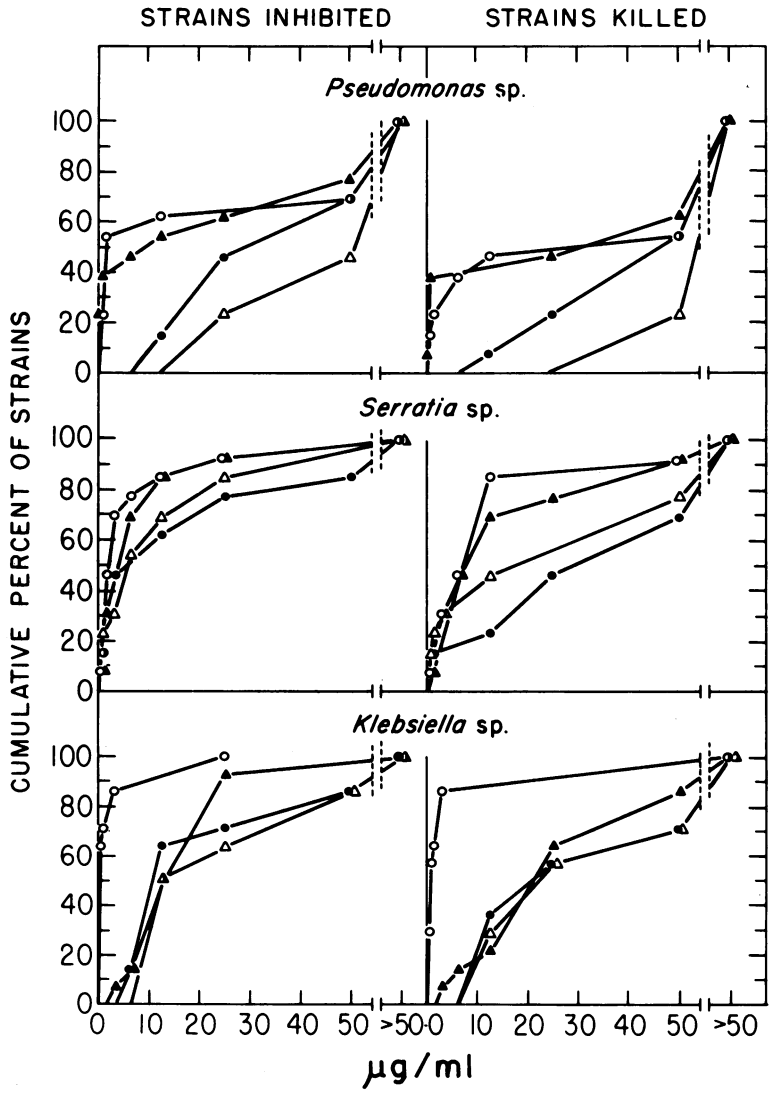

FIG. 1. *Activity of netilmicin against 13 strains each of Pseudomonas sp. and Serratia sp. and 17 strains of Klebsiella sp. resistant to either sisomicin, gentamicin, or tobramycin. Symbols: (○) netilmicin, (●) sisomicin; (△) gentamicin; (▲) tobramycin.*

TABLE 2. *Susceptibility to netilmicin (N) of gram-negative isolates resistant to either sisomicin (S), gentamicin (G), or tobramycin (T)*

Isolate	MIC (μg/ml)				MBC (μg/ml)			
	N	S	G	T	N	S	G	T
Enterobacter sp.								
A.A. 676	0.78	>12.5	>12.5	1.56	3.12	>12.5	>12.5	6.25
A.Cl. 314	1.56	>12.5	>12.5	6.25	3.12	>12.5	>12.5	12.5
Proteus sp. (indole positive)								
101	>50	>50	>50	>50	>50	>50	>50	>50
494	6.25	6.25	6.25	1.56	6.25	6.25	6.25	6.25
168	50	>50	>50	12.5	>50	>50	>50	>50
172	50	>50	>50	12.5	50	>50	>50	12.5
Acinetobacter sp.								
988	>50	25	>50	12.5	>50	25	>50	12.5
163	>50	25	>50	12.5	>50	25	>50	12.5
444	>50	25	>50	6.25	>50	25	>50	12.5
Providencia sp.								
185	50	6.25	50	12.5	50	6.25	50	50
196	>50	>50	>50	>50	>50	>50	>50	50
E. coli								
170	50	>50	>50	25	50	>50	>50	>50
173	25	>50	>50	50	50	>50	>50	50
175	25	>50	>50	50	50	>50	>50	>50
180	3.12	1.56	3.12	6.25	3.12	3.12	3.12	12.5
181	50	>50	>50	>50	>50	>50	>50	>50
193	>50	>50	>50	>50	>50	>50	>50	>50

cin in in vitro studies against gram-negative isolates, especially against gentamicin-resistant bacteria, suggests that this new aminoglycosidic aminocyclitol warrants clinical investigation for the treatment of patients with infections due to gram-negative bacteria, especially those resistant to gentamicin.

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