ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1977, p. 362-364

Vol. 11, No. 2
Printed in U.S.A.

In Vitro Activity of Netilmicin

J. A. SMITH,* J. R. MORGAN, AND M. MOGYOROS

Division of Microbiology, Mount Sinai Hospital, and Departments of Medical Microbiology and Medicine, University of Toronto, Toronto, Ontario, Canada*

Received for publication 27 September 1976

The activity of netilmicin against a variety of bacteria was similar to that of gentamicin, sisomicin, and tobramycin, but it was less active than these three drugs against *Pseudomonas aeruginosa*. Synergy with penicillin G against enterococci was demonstrated.

Netilmicin is a derivative of sisomicin by the addition of an ethyl radical at the 1-N position on the deoxystreptamine moiety. Preliminary animal studies by the manufacturer (Schering Corp.) suggest that threshold toxicity to kidney and vestibular apparatus occurs at a serum concentration up to five times that of gentamicin. Comparative studies of the in vitro antimicrobial activities of aminoglycosides have suggested that the parent compound sisomicin is equal in activity to, or more active than, gentamicin (1-3). This study evaluates the in vitro activity of netilmicin against 337 strains of aerobic gram-negative rods, including *Pseudomonas aeruginosa* (117 strains, of which 41 were resistant to 8 μg/ml), *Escherichia coli* (73 strains), *Klebsiella* spp. (73 strains), *Enterobacter* spp. (20 strains), *Citrobacter* spp. (10 strains), and *Proteus mirabilis* (40 strains). In addition, the drug was tested against *Staphylococcus aureus* (30 strains) and enterococcus (29 strains).

All strains were tested against netilmicin, sisomicin, tobramycin, amikacin, and gentamicin. Minimum inhibitory concentrations were determined on Mueller-Hinton agar using the Steers multiple inoculator (6) and a broth inoculum containing 10^8 colony-forming units/ml. The antibiotic concentrations used were 0.2, 0.4, 0.8, 1.6, 3.0, 5.0, 8.0, 10.0, 15.0, and 20.0 μg/ml. Cumulative percentages of susceptibility to the various antibiotic concentrations were plotted for each strain, and from these graphs were calculated the concentrations required to inhibit 50 and 90% of the strains.

Against *E. coli*, all five aminoglycosides exhibited almost identical activity with the exception of amikacin, which was slightly less active (Table 1). Netilmicin and sisomicin equalled the activity of gentamicin against 50% of strains of *Klebsiella* spp. (Table 1). However, 98% of the *Klebsiella* strains tested were inhibited by 0.8 μg of sisomicin per ml as compared to 1.6 μg each of netilmicin and gentamicin per ml.

Although the total number of strains of *Enterobacter* spp. and *Citrobacter* spp. (Table 1) was small, the results suggest that netilmicin and sisomicin were more active than the other antibiotics tested. There seemed little apparent difference between the activity of all five aminoglycosides against *P. mirabilis* (Table 1), which is at variance with the findings of Levison and Kaye (2), who ascribed greater activity to gentamicin and sisomicin than to tobramycin and amikacin.

Netilmicin displayed significantly less activity than the other antibiotics against *P. aeruginosa* (Table 2).

All strains of *S. aureus* tested were inhibited by 0.2 μg of each antibiotic per ml, except amikacin, which required 3 μg/ml to inhibit 100% of *S. aureus* strains. Netilmicin, sisomicin, and gentamicin showed activity against enterococcus (Table 1). In particular, at 10 μg/ml, 49% of strains were inhibited by netilmicin, whereas only 7% were inhibited by gentamicin; the other aminoglycosides were ineffective. This prompted an investigation of the synergistic activity of gentamicin (5 μg/ml) and netilmicin (5 μg/ml), respectively, in combination with penicillin (20 μg/ml) against 15 strains of *Streptococcus faecalis* and 1 strain of *Streptococcus faecium*. The method used was that of timed killing curves as described by Moellering et al. (4, 5).

Synergy was demonstrated with both drug combinations against 14 of 15 strains of *S. faecalis*; the remaining strain was completely killed by gentamicin alone at 24 h. Synergy was demonstrated between penicillin and netilmicin against all strains of *S. faecalis* and against the single strain of *S. faecium*. One strain of *S. faecalis* was particularly susceptible to genta-

TABLE 1. *Concentrations of antibiotics at which 50 and 90% of strains tested were inhibited*

Organism	No. of strains	Concn (μg/ml) of antibiotic for inhibition of:									
		50% of strains					90% of strains				
		Gentamicin	Tobramycin	Amikacin	Sisomicin	Netilmicin	Gentamicin	Tobramycin	Amikacin	Sisomicin	Netilmicin
P. aeruginosa	117	2.1	1.6	4.75	1.45	6.75	>20	>20	>20	>20	>20
E. coli	73	0.55	0.6	0.65	0.6	0.7	1.4	1.45	3.8	1.6	1.6
Klebsiella	73	0.35	0.7	0.95	0.35	0.35	1.2	1.5	1.55	0.7	1.1
Proteus mirabilis	44	2.0	1.4	2.3	0.6	1.2	2.85	2.75	2.95	2.5	2.0
Citrobacter spp.	10	1.3	1.8	1.6	0.4	0.4	3.0	3.0	2.0	0.8	1.6
Enterobacter	20	0.4	0.7	1.1	0.5	0.3	1.3	2.3	2.7	0.7	0.8
Enterococcus	29	12.1	>20	>20	11.9	10	14.2	>20	>20	15	15
S. aureus	30	<0.2	<0.2	1.8	<0.2	<0.2	<0.2	0.3	2.8	<0.2	<0.2

TABLE 2. *Cumulative percentages of susceptibility of 117 strains of P. aeruginosa to five aminoglycosides*

Aminoglycoside	% Susceptibility at antibiotic concn (μg/ml) of:									
	0.2	0.4	0.8	1.6	3	5	8	10	15	20
Gentamicin	0.85	4.2	30.7	47.0	56.4	60.6	64.9	67.5	79.4	82.0
Tobramycin	1.7	25.6	46.1	50.4	64.9	66.6	71.7	73.5	74.3	76.9
Amikacin	0.85	1.7	17.0	33.3	35.8	52.1	60.0	67.5	75.2	82.9
Sisomicin	1.7	17.9	34.1	54.7	64.1	67.5	68.3	70.0	74.3	74.3
Netilmicin	0	2.5	7.6	18.8	24.7	42.7	55.5	60.6	64.9	67.5

micin, so that synergy as defined (4, 5) could not be demonstrated at 24 h, but there was a 3-log difference in the number of surviving bacteria at 4 h when either combination was compared with the best single drug.

As previously reported (1-3), the activities of gentamicin, tobramycin, and sisomicin do not differ greatly from each other and netilmicin appears to follow a similar pattern of activity against aerobic gram-negative rods, but with the important difference that netilmicin is significantly less active against *P. aeruginosa*.

We would like to acknowledge the technical assistance of L. Tiosejo, R. Kapun, and J. Campbell and the financial support of Schering Corp. (Canada).

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