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Sisomicin Versus Netilmicin: In Vitro Susceptibility Testing

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Antimicrobial susceptibility to sisomicin and netilmicin (Sch 20569) was determined on 164 clinical isolates using a broth microdilution method. Sisomicin was active against 86.1%, and netilmicin against 96.4%, of the isolates. In addition, netilmicin was active against 93.7% of the strains that were resistant to gentamicin, kanamycin, tobramycin, and sisomicin.

Gentamicin is used often in the treatment of bacterial infections. Two significant factors can be associated with gentamicin usage: the increased occurrence of resistant strains and toxicity. These factors have stimulated studies on new drugs that could potentially replace gentamicin or be used whenever gentamicin cannot. This study compared the susceptibility of clinical isolates to two new aminoglycosides, sisomicin and netilmicin. Netilmicin is a semisynthetic derivative of sisomicin, which is produced by *Micromonospora inyoensis*. Netilmicin and sisomicin closely resemble gentamicin in molecular structure.

The organisms studied were initial clinical isolates identified by conventional methods in the clinical microbiology section of the Oklahoma City Veterans Administration Hospital.

Antibiotic powders of sisomicin and netilmicin were donated by the Schering Corp. Antimicrobial disks, used for agar diffusion testing, were obtained commercially.

Minimal inhibitory concentrations (MICs) were determined by a broth microdilution method. Mueller-Hinton broth (Difco) was used as the diluent. The final volume in each microtiter plate well was 0.1 ml. Microtiter plates were incubated for 16 to 18 h at 35°C after inoculation. The MIC was taken as the highest dilution of antimicrobial in which no visible growth appeared. MICs of 4 μg or less per ml were considered as indicative of susceptibility for sisomicin and netilmicin. Disk agar diffusion studies were performed by the method of Bauer et al. (1).

Table 1 notes the MICs performed on 156 isolates. The median MICs for sisomicin and netilmicin were similar for most isolates except *Serratia marcescens* and *Proteus* sp. other than *Proteus mirabilis*. Netilmicin was significantly more active in the former group. The following isolates were not mentioned in Table 1: two strains of *Micrococcus* sp., two *Pseudomonas* sp., one *Citrobacter freundii*, one *Providencia* sp., and two *Acinetobacter calcoaceticus*. Their range of susceptibility was from 4 to ≤0.125 μg/ml.

Disk diffusion susceptibility studies on 164 isolates showed: gentamicin (88.5% susceptible), kanamycin (58.8%), tobramycin (86.7%), and sisomicin (89.1%). Susceptibility testing results to gentamicin and sisomicin were identical in 161 (97.5%) of the isolates. Sixteen isolates were resistant to gentamicin, kanamycin, tobramycin, and sisomicin. Fifteen of these strains were resistant to sisomicin and susceptible to netilmicin as determined by MIC studies (Table 2). One isolate, *Proteus rettgeri* F21, was resistant to both sisomicin and netilmicin. This isolate was susceptible to amikacin as determined by disk agar diffusion testing. Twelve of the sixteen strains were isolated from urinary tract sources.

The similarity of gentamicin and sisomicin has been previously mentioned (2, 5, 8, 9). However, netilmicin has been reported to be significantly more active than gentamicin against clinical isolates of *Enterobacteriaceae, Staphylococcus aureus*, and *Pseudomonas aeruginosa* (6). Another study (4) showed netilmicin to be effective against gentamicin-resistant *Enterobacteriaceae*. This report discloses netilmicin to be significantly more active than sisomicin. These differences in activity appear to be the result of distinct enzymes. Kabins et al. (4) found that gentamicin-resistant organisms possess an aminoglycoside-adenylating enzyme, whereas netilmicin resistance was associated with an acetylating enzyme. They also reported that *Proteus* sp. have an acetylating enzyme, which may explain (Table 2) higher MICs for two aminoglycoside-resistant *Proteus rettgeri* in this study. Since the MICs for *Proteus mirabilis* were lower than those for other *Proteus* sp. (Table 1), the presence of acetylating enzymes may differ in the two groups.

This investigation shows *P. aeruginosa* to be susceptible to netilmicin, as determined by

TABLE 1. *Comparison of in vitro activity of sisomicin (S) and netilmicin (N)*

Organism	No. of strains	Drug	MIC, μg/ml	
			Range	Median
Staphylococcus aureus	25	S	≤0.125–0.5	≤0.125
		N	≤0.125–0.5	≤0.125
Staphylococcus epidermidis	6	S	All≤0.125	≤0.125
		N	All≤0.125	≤0.125
Group D enterococcus	8	S	1–8	8
		N	2–8	4
Pseudomonas aeruginosa	29	S	≤0.125–1	≤0.125
		N	≤0.125–2	0.25
Escherichia coli	30	S	≤0.125–128	0.25
		N	≤0.125–2	0.25
Klebsiella pneumoniae	16	S	All≤0.125	≤0.125
		N	≤0.125–0.25	≤0.125
Enterobacter	14[a]	S	≤0.125–32	≤0.125
		N	≤0.125–1	≤0.125
Serratia marcescens	7	S	≤0.125–>128	32
		N	≤0.125–2	0.25
Proteus mirabilis	14	S	≤0.125–4	0.25
		N	≤0.125–2	0.50
Proteus, other	7[b]	S	≤0.125–64	0.50
		N	≤0.125–16	4

[a] Includes nine *Enterobacter aerogenes*, two *E. agglomerans*, and three *E. cloacae* isolates.
[b] Includes one *Proteus morganii*, four *P. rettgeri*, and two *P. vulgaris* isolates.

TABLE 2. *MICs of aminoglycoside-resistant isolates*

Isolate	MIC, μg/ml	
	Sisomicin	Netilmicin
Escherichia coli H4	16.0	0.5
Enterobacter aerogenes D6	32.0	1.0
Serratia marcescens B8	128.0	2.0
E. coli C9	16.0	1.0
S. marcescens E9	128.0	1.0
Proteus rettgeri F9	32.0	4.0
Enterobacter agglomerans A10	16.0	0.5 0
E. coli E12	16.0	≤0.125
S. marcescens C14	32.0	0.25
S. marcescens F15	32.0	0.25
E. agglomerans A17	16.0	≤0.125
E. coli C17	32.0	0.5
E. cloacae A20	16.0	0.5
P. rettgeri F21	64.0	16.0
S. marcescens A24	>128.0	2.0
E. coli G24	128.0	1.0

broth dilution studies. Kabins et al. (4) noted a higher degree of *P. aeruginosa* susceptibility when MICs were done in broth than agar. Which is the most representative method relating to in vivo activity? Is *P. aeruginosa* generally susceptible or resistant to netilmicin in vivo? Two reports (3, 7) have suggested that MICs performed in agar are more clinically significant due to the greater similarity of cation concentration between agar and serum than broth and serum. In vivo studies involving *P. aeruginosa* infections would help to answer these questions.

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