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In Vitro Comparison of Gentamicin, Tobramycin, Sisomicin, and Netilmicin

K. N. BROWN,* J. BENEDICTSON, AND S. SWANBY

Department of Laboratories, Foothills Hospital, Calgary, Alberta, T2N 2T9 Canada

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The antimicrobial activity of gentamicin, tobramycin, sisomicin, and netilmicin (Sch 20569) was compared against 150 strains of organisms. Netilmicin was shown to be the least effective against *Pseudomonas* strains but to have slightly better activity against *Staphylococcus aureus* and *Escherichia coli* than the other agents. The effect of calcium and magnesium in enhancing the differences in activity of these aminoglycosides against *Pseudomonas* strains was also demonstrated.

This study was carried out to compare the in vitro antibacterial activity of four aminoglycoside antibiotics, gentamicin, tobramycin, sisomicin, and netilmicin (Sch 20569), against 148 clinical isolates and two control strains. There were 50 strains each of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*. The control organisms used were *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922.

Minimum inhibitory concentrations (MICs) were determined in the conventional manner in three types of broth: (i) brain heart infusion broth (BHI; BBL 11063) with added calcium and magnesium to provide levels of 75 and 20 mg/liter, respectively; (ii) BHI broth (BBL 11063) unmodified (calcium and magnesium levels were 36 and 14 mg/liter, respectively); and (iii) tryptone broth (Oxord L42). A medium control with no antibiotic added was provided for each organism tested to assure viability, and medium controls with no antibiotic and no organism were also used to assure sterility of the medium. Type (i) broth was used for *Pseudomonas* strains, type (ii) was used for *E. coli* strains, and type (iii) was used for *S. aureus* strains.

Each tube, other than the medium controls, was inoculated with approximately 10^4 colony-forming units of the organism under test.

The results of the MICs of the four antibiotics against these groups of organisms are shown in Fig. 1 (*P. aeruginosa*), Fig. 2 (*S. aureus*), and Fig. 3 (*E. coli*). These illustrate the relationship between MICs and cumulative percentages of strains inhibited.

The most pronounced differences are shown with regard to *P. aeruginosa* (Fig. 1). At the concentration inhibiting 50% of the strains, the MIC of tobramycin was 0.48 μg/ml and that of netilmicin (Sch 20569) was 3.6 μg/ml, whereas gentamicin and sisomicin were almost inseparable at 1.35 and 1.45 μg/ml, respectively. In effect, therefore, a sevenfold difference in activity between tobramycin and netilmicin was demonstrable against this group of *Pseudomonas* strains isolated using BHI broth with added calcium and magnesium.

Figure 2, however, illustrates the converse, in that for the group of staphylococcal isolates tested, the 50% inhibition level was 0.01 μg of netilmicin (Sch 20569) and 0.03 μg of tobramicin per ml, indicating a threefold difference in activity, but in this instance with netilmicin showing the advantage. Gentamicin and sisomicin occupied intermediate positions in their activity.

Netilmicin (Sch 20569) also showed an increase in activity compared with the other aminoglycosides tested against the group of *E. coli* strains, although this difference was less marked. This is shown in Fig. 3. The MICs of netilmicin (Sch 20569) and gentamicin at the 50% inhibition level were 3 and 5 μg/ml, respectively, with tobramycin and sisomicin occupying intermediate positions. These results obtained with gentamicin, tobramycin, and sisomicin are in accord with the work of other investigators who have evaluated these aminoglycosides (1, 2, 5, 6).

Sixteen strains of *P. aeruginosa* were selected from a group of 50. These represented eight gentamicin-susceptible strains and eight gentamicin-resistant strains. These were tested for their MICs to gentamicin, tobramycin, sisomycin, and netilmicin as before, but without added calcium and magnesium in the BHI broth. Therefore, the calcium and magnesium levels were 36 and 14 mg/liter, respectively. For the 16 strains tested, it was demonstrated that

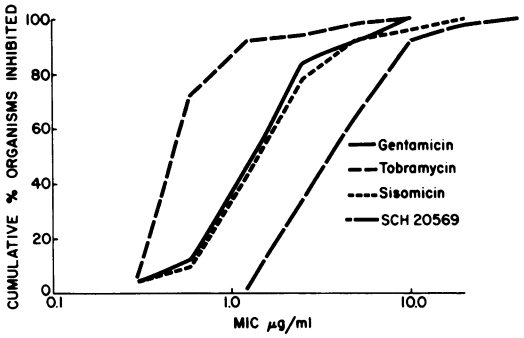

FIG. 1. *MICs of the four antibiotics against P. aeruginosa strains.*

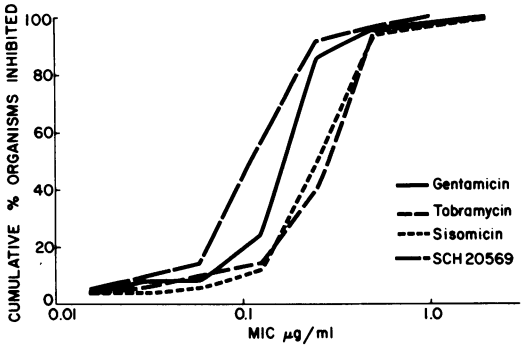

FIG. 2. *MICs of the four antibiotics against S. aureus strains.*

at the 50% inhibition level the MIC range of tobramycin and netilmicin was increased from 0.42 to 1.5 μg/ml without calcium and magnesium to 0.42 to 5.8 μg/ml with added calcium and magnesium. Therefore, the addition of calcium and magnesium apparently increased the differences in activity between tobramycin and netilmicin from three- to sevenfold.

Differences in MICs of gentamicin against *P. aeruginosa* strains have been related to calcium and magnesium concentrations by other workers (3, 4). Our work demonstrates that the addition of calcium and magnesium to BHI broth increased the apparent differences in activity of the antimicrobials tested.

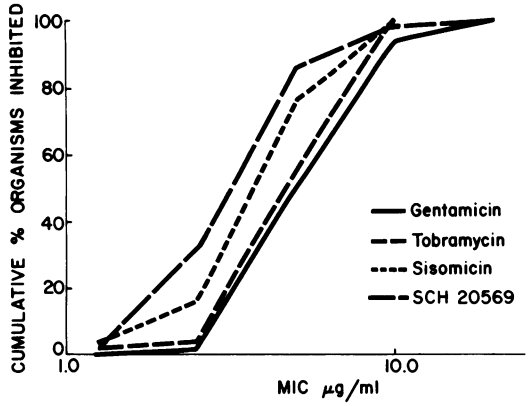

FIG. 3. *MICs of the four antibiotics against E. coli.*

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