Bactericidal Efficacy of Sch 20569 and Amikacin Against Gentamicin-Sensitive and -Resistant Organisms

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Sch 20569 is a semisynthetic derivative of gentamicin with activity against many gentamicin-resistant gram-negative bacilli. We compared its bactericidal action with that of gentamicin and amikacin against 171 clinical isolates of Enterobacteriaceae, Staphylococcus aureus, and Pseudomonas aeruginosa. Sch 20569 and amikacin showed markedly greater activity than gentamicin against Escherichia coli, Klebsiella, Enterobacter, Citrobacter, and indole-positive Proteus, primarily by virtue of their lethal effect on gentamicin-resistant strains (minimal bactericidal concentration ≥ 12.5 μg/ml). Indole-negative Proteus isolates were uniformly sensitive to Sch 20569, whereas several were resistant to both gentamicin and amikacin. Amikacin was most active against Providencia, as was gentamicin against Serratia. All three agents exhibited similar activity against Pseudomonas. Staphylococcus aureus was more sensitive to gentamicin and Sch 20569 than to amikacin.

Sch 20569 is a new semisynthetic aminoglycoside derived from sisomycin, an antibiotic produced by the growth of Micromonospora inyoensis. In molecular structure, both Sch 20569 and sisomycin most closely resemble gentamicin C12, a component of the gentamicin complex (Fig. 1). Because we have encountered an increasing number of gentamicin-resistant gram-negative infections at the Manhattan V.A. Hospital (5), we studied the bactericidal efficacy of this new aminoglycoside and amikacin against both gentamicin-sensitive and -resistant clinical isolates.

MATERIALS AND METHODS

Groups of twenty isolates of Escherichia coli, Klebsiella, Enterobacter, Serratia, Proteus, Pseudomonas, and Staphylococcus aureus; and 11 strains of Citrobacter were chosen for comparative tube dilution sensitivities against gentamicin, amikacin, and Sch 20569. Minimal inhibitory and bactericidal concentrations (MIC and MBC, respectively) were assayed by tube dilution in 1-ml volumes of Mueller-Hinton broth, using each antibiotic in simultaneous tests against a single isolate. Based upon prior studies with aminoglycoside antibiotics (4), it was assumed that the constant cation content of a single lot of Mueller-Hinton broth would affect the activity of each antibiotic equally. The MBC was defined as that concentration which killed >99% of 10⁶ organisms in 18 h as demonstrated by subculture onto drug-free solid media. The difference between MIC and MBC values was one or two tube dilutions in the majority of instances; thus, only the MBC values will be presented. Resistance to gentamicin or Sch 20569 is defined as an MBC ≥ 12.5 μg/ml; amikacin resistance is defined as an MBC ≥ 25 μg/ml.

RESULTS

E. coli. Figure 2 shows that Sch 20569 had fourfold greater activity than amikacin against many strains of E. coli and that both were quite effective against all 13 gentamicin-resistant strains. Against sensitive strains, the activity of gentamicin and Sch 20569 was almost identical.

Klebsiella. Similar results were obtained with Klebsiella (Fig. 3). Again, all gentamicin-resistant strains were sensitive to both Sch 20569 and amikacin.

Enterobacter. Figure 4 demonstrates that the MBCs of Sch 20569 and amikacin were more nearly identical against Enterobacter. Both showed good bactericidal activity against almost all gentamicin-resistant isolates.

Serratia. The results with Serratia were quite different (Fig. 5). We had six strains with MBCs of gentamicin which were 25 to 50 μg/ml or more. All were similarly resistant to Sch 20569 and the MBCs of three were ≥ 25 μg/ml for amikacin. Further, those which were sensitive to gentamicin were far more sensitive than to either of the other two drugs.

Citrobacter. Eleven Citrobacter strains were...
SISOMICIN (R=H)
Sch 20569 (R=C$_2$H$_5$)

**FIG. 1.** Basic chemical structure of sisomycin and Sch 20569. Sisomycin differs from gentamicin $C_{18}$ only by the presence of a single ethyl group.

E. Coli

**Fig. 2.** MBCs of Sch 20569 (569), amikacin, and gentamicin for 20 strains of $E$. coli.

tested, most of which were resistant to gentamicin. All were relatively sensitive to Sch 20569 and amikacin (Fig. 6).

**Indole-positive Proteus.** Most gentamicin-resistant, indole-positive $Proteus$ strains were sensitive to the two newer aminoglycosides. However, three of thirteen required an MBC of $\geq 12.5 \mu g/l$ of Sch 20569, and one required an MBC of 25 $\mu g/ml$ of amikacin. Gentamicin-sensitive isolates showed similar susceptibility to all three drugs (Fig. 7).

**Indole-negative Proteus.** Surprisingly, amikacin showed slightly less activity than gentamicin against a small number of relatively resistant indole-negative $Proteus$ strains. In contrast, the MBCs of Sch 20569 were all within the sensitive range (Fig. 8).

**Providencia.** Providencia strains in our hospital are almost all relatively resistant to gentamicin, most frequently demonstrating a fourfold difference between MIC and MBC against this antibiotic. The results with Sch 20569 were almost identical, whereas amikacin demonstrated a two- to fourfold greater bactericidal activity against all strains (Fig. 9).

**Pseudomonas aeruginosa.** Unlike the Enter-
Enterobacteriaceae, *Pseudomonas* susceptibility to gentamicin in our hospital does not show a sharp division between sensitive and resistant strains. Rather, a continuum exists between strains killed by 0.78 to 1.56 \( \mu \text{g/ml} \) and those requiring 25 to 50 \( \mu \text{g/ml} \). Amikacin and Sch 20569 sensitivities show the same effect with somewhat less activity than gentamicin against all strains (Fig. 10).

*Staphylococcus aureus.* *S. aureus* is known to be susceptible to gentamicin in vitro, although this antibiotic is not recommended for primary treatment of such infections. Sch 20569 is somewhat less active against the staphylococcus, and amikacin demonstrated a further decrease in bactericidal activity (Fig. 11).

**DISCUSSION**

These studies provide encouraging data suggesting that Sch 20569 may be a highly useful antibiotic, particularly for infections caused by gentamicin-resistant *Enterobacteriaceae*. Unfortunately, neither Sch 20569 nor amikacin appears to have greater activity against *Pseudomonas* than does gentamicin. Conversely, tobramycin has been shown to affect some strains of gentamicin-resistant *Pseudomonas* (1, 2), whereas our earlier studies demonstrated no susceptibility of gentamicin-resistant *Klebsiella* and *Enterobacter* strains to tobramycin (5). Finally, gentamicin appears to be more effective against *Serratia* than either of the two newer drugs tested.

Blood levels of Sch 20569 in animals are comparable to those of gentamicin (6), whereas blood levels achieved by therapeutic doses of amikacin (15 to 20 \( \mu \text{g/ml} \)) are higher than those from either Sch 20569 or gentamicin (5 to 10 \( \mu \text{g/ml} \)) (3). This corresponds to an approximate twofold difference in MBC which is within experimental error of the method. Nevertheless, differences in in vitro activity between amikacin and the other two drugs studies must be evaluated in relation to higher achievable blood concentrations.
levels of amikacin. For example, fourfold lower MBCs of Sch 20569 as compared with amikacin against several E. coli strains would be reduced in potential therapeutic significance by twofold higher blood levels of the latter drug. Similarly, Pseudomonas strains requiring an MBC of 12.5 μg/ml of gentamicin, Sch 20569 or amikacin may prove more susceptible in vivo to amikacin. The second major factor which will influence the relative clinical usefulness of Sch 20569 is its human toxicity. Animal studies to
date suggest significantly less oto- and nephrotoxicity than gentamicin in 14-day and 90-day chronic studies using the rat, dog, and cat (6). Acute toxicity studies in the mouse, rat, and dog suggest greater toxicity than gentamicin, probably as a result of greater neuromuscular blocking action at high doses (6).

In conclusion, the in vitro bactericidal activity of Sch 20569 suggests that this semisynthetic aminoglycoside may provide significant advantages over currently available antibiotics and warrants careful clinical evaluation.

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LITERATURE CITED