NOTES

COMPARATIVE *IN VITRO* ACTIVITY OF A SEMISYNTHETIC DERIVATIVE OF GENTAMICIN B (SCH 21420) AND FIVE OTHER AMINOGLYCOSIDES

CHATRCHAI WATANAKUNAKORN

Infectious Disease Division, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267, U.S.A.

(Received for publication June 19, 1978)

With the increasing prevalence of Gram-negative bacilli resistant to existing aminoglycosides, new semisynthetic aminoglycosides with more potent *in vitro* activity or with effectiveness against resistant bacteria are continually being developed. Sch 21420 is 1-N-[(S)-3-amino-2-hydroxypropionyl]-gentamicin B, a new semisynthetic compound developed in the research laboratories of Schering Corporation (T.L. NAGABHUSHAN, A. B. COOPER, H. TSAI and P. J. L. DANIELS. Programs & Abstracts, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, abstr. no. 249, 1977).

There have been two preliminary studies of the *in vitro* activity of this compound[1] (K. P. FU and H. C. NEU. Programs & Abstracts, 17th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, abstr. no. 250, 1977). In this study, the *in vitro* activity of Sch 21420 against both gentamicin-resistant and gentamicin-susceptible Gram-negative bacilli was compared with that of gentamicin, tobramycin, sisomicin, netilmicin and amikacin.

All Gram-negative bacilli used in this study were isolated from clinical materials. The gentamicin-resistant (MIC > 4 μg/ml) strains consisted of *Pseudomonas aeruginosa* (17 strains), *Pseudomonas* species (10 strains), *Klebsiella* species (7 strains), *Serratia* species (6 strains), *Enterobacter* species (6 strains), *Proteus* species (9 strains), *Providencia* species (14 strains) and *Escherichia coli* (6 strains). Also tested were 41 strains of gentamicin-susceptible (MIC $\leq$ 4 μg/ml) Enterobacteriaceae which included *Klebsiella* species (8 strains), *Serratia* species (9 strains), *Enterobacter* species (9 strains), *Proteus* species (5 strains), *Providencia* species (1 strain) and *E. coli* (9 strains).

The MIC of Sch 21420, gentamicin, tobramycin, sisomicin, netilmicin, and amikacin was determined simultaneously by the WHO-ICS agar dilution method[2]. MUELLER-HINTON agar

Table 1. Cumulative percent susceptibility of gentamicin-resistant Gram-negative bacilli to 6 aminoglycosides

	No. tested	Antibiotic concentration in μg/ml							
		0.5	1	2	4	8	16	32	64
Pseudomonas	27								
Gentamicin						26	37	37	48
Tobramycin			15	56	67	67	78	89	93
Sisomicin			15	30	41	41	41	48	59
Netilmicin		4	7	11	11	15	56	81	89
Amikacin				7	26	67	85	89	96
Sch 21420			7	11	30	44	89	89	96
Enterobacteriaceae	48								
Gentamicin						13	40	75	94
Tobramycin					4	6	35	69	92
Sisomicin				4	29	71	90	100	
Netilmicin		4	13	23	33	40	58	77	85
Amikacin			2	40	58	75	79	83	85
Sch 21420		2	6	33	60	71	83	85	85

Table 2. Cumulative percent susceptibility of 41 strains of gentamicin-susceptible Enterobacteriaceae to 6 aminoglycosides

Antibiotic	Antibiotic concentration in μg/ml							
	≤0.25	0.5	1	2	4	8	16	32
Gentamicin	2	34	73	93	100			
Tobramycin		20	59	76	95	100		
Sisomicin	50	80	98	100				
Netilmicin		5	29	76	95	100		
Amikacin				29	71	88	100	
Sch 21420			7	61	78	95	98	100

was used. The inoculum was 0.002 ml of a 10^{-2} dilution of an overnight culture (approximately $10^3 \sim 10^4$ organisms) delivered by a STEERS replicator[3]. For a given isolate, the same inoculum was used to inoculate all 6 series of agar plates incorporated with serial two-fold dilutions of antibiotics from 64 to 0.25 μg/ml. An agar plate with no antibiotic served as a control. Plates were incubated at 37°C for 24 hours. The MIC was defined as the lowest concentration of antibiotic allowing no growth or growth of only one colony.

Table 1 shows the comparative *in vitro* activity of all 6 aminoglycosides against gentamicin-resistant *Pseudomonas* (27 strains) and Enterobacteriaceae (48 strains). For *Pseudomonas*, the most active compound was tobramycin. However, Sch 21420 as well as amikacin and sisomicin were effective against a large number of gentamicin-resistant *Pseudomonas*. Netilmicin was the least active compound. As for gentamicin-resistant Enterobacteriaceae, Sch 21420 and amikacin had similar activity and were the most active compounds. Sisomicin and netilmicin were also effective against some gentamicin-resistant organisms, but cross-resistance between gentamicin and tobramycin was complete.

Results of the 41 strains of gentamicin-susceptible Enterobacteriaceae are shown in Table 2. Sisomicin was the most active compound. Tobramycin and netilmicin were not as active as gentamicin. On the weight basis, Sch 21420 was similar to amikacin but there were more strains susceptible to low concentration of Sch 21420 than amikacin.

The results of this investigation indicated that the activity of Sch 21420 was similar to that of amikacin and that Sch 21420 was active against large numbers of gentamicin-resistant *Pseudomonas* and Enterobacteriaceae. For gentamicin-susceptible Enterobacteriaceae, Sch 21420 had no advantage over gentamicin.

The investigation was supported by a grant from Schering Corporation, Bloomfield, N. J., and the Morton Hamburger Memorial Fund. CHERYL GLOTZBECKER and DEXTER BALTERMAN provided excellent technical assistance.

References

1) YU, P. K. W. & J. A. WASHINGTON II: *In vitro* evaluation of a semisynthetic derivative of gentamicin B (Sch 21420). Antimicr. Agents & Chemoth. 13: 891~892, 1978
2) ERICSSON, H. M. & J. C. SHERRIS: Antibiotic sensitivity testing: report of an international collaborative study. Acta Pathol. Microbiol. Scandi. Section B 217 (suppl.): 1~90, 1971
3) STEERS, E.; E. L. FOLTZ, B. S. GRAVES & J. RIDEN: An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. Antibiot. & Chemoth. 9: 307~311, 1959