BIOLOGICAL ACTIVITY OF SCH 21420, THE 1-*N*-*S*-α-HYDROXY-β-AMINOPROPIONYL DERIVATIVE OF GENTAMICIN B

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(Received for publication April 8, 1978)

Sch 21420, the 1-*N*-HAPA derivative of gentamicin B, has been compared to gentamicin, tobramycin and amikacin in a variety of *in vitro* and *in vivo* tests. Based on studies with a large number of sensitive and resistant bacteria, it was shown that Sch 21420 has a spectrum and potency essentially the same as that of amikacin. Serum levels in mice, rats, and dogs are similar to those of other aminoglycosides. Sch 21420 was found to be markedly less toxic than amikacin in chronic renal function tests in rats and thus appears to have an advantageously improved therapeutic index compared to amikacin.

In recent years, a number of semi-synthetic aminoglycosides have been described with improved spectrum of activity against an increasing number of aminoglycoside-resistant strains. The ability of amikacin to resist a number of types of inactivating mechanisms led us to evaluate a series of analogous derivatives of gentamicin B (Sch 14342). Gentamicin B was chosen because of its favorable chronic toxicity profile in laboratory animals[1]. Among a large number of such derivatives prepared, Sch 21420, the 1-*N*-*S*-α-hydroxy-β-aminopropionyl derivative of gentamicin B[2] was chosen as the most promising for further study. This report presents results of laboratory studies of Sch 21420 in comparison with gentamicin, tobramycin and amikacin.

Materials and Methods

Sch 21420 and gentamicin were used as sulfate salts, and all results are expressed in terms of base activity, as determined by bioassay. Tobramycin, provided by Eli Lilly and Co., and amikacin, provided by Bristol Laboratories, were used as the bases. Methods used were generally similar to those reported earlier[3,4].

In vitro Activity

In vitro activity was studied using an agar dilution method on MUELLER-HINTON agar. An inoculum of approximately $10^3 \sim 10^4$ organisms was delivered onto the agar surface from an overnight culture in MUELLER-HINTON broth using the inocula replicating apparatus of STEERS *et al*[5]. The minimal inhibitory concentration (MIC) was defined as the lowest concentration at which less than six discrete colonies were visible. *In vitro* activity was also studied by means of conventional broth dilution tests with MUELLER-HINTON broth as the medium. The inoculum used was 0.05 ml of a 1 : 1000 dilution of an overnight culture; the volume of medium in each tube was 3 ml. The MIC was defined as the lowest concentration that prevented visible growth. *In vitro* bactericidal activity was assessed in a manner similar to the broth MIC determinations. After a 24-hour incubation, the tubes containing the lowest concentration of antibiotic allowing growth and the three next highest concentrations of antibiotic were streaked onto the surface of MUELLER-HINTON agar. After a 48-hour incubation, the minimum bactericidal concentration (MBC) was read as the lowest concentration preventing visible growth on the plates.

In vivo Tests

Mouse protection tests and acute toxicity tests were performed with groups of seven male CFI

mice weighing approximately 20 g each. In the protection tests, mice were dosed once subcutaneously one hour after intraperitoneal infection with approximately 10^7 organisms/mouse. Usually, five to seven dose levels were used in each test, and mean protective dose (PD_{50}) values were calculated by probit procedures using survivors 48 hours after infection. Comparative studies were always carried out simultaneously using the same inoculum.

Serum levels in mice (CFI, 20 g each) were determined following a s.c. dose. Blood was taken by deep cervical incision from groups of three mice and pooled for serum assay.

Serum levels in rats (Sprague-Dawley, 200 g each) were determined following a s.c. dose of 50 mg/kg. Blood was taken from rats anesthetized with ether, by cardiac puncture. Blood from groups of three rats was pooled for serum assay.

Serum levels in dogs (male beagles, 10 kg each) were determined following a single i.v. dose of 10 mg/kg. For evaluation of nephrotoxicity potential, Sch 21420 was compared directly with gentamicin and amikacin. Male Sprague-Dawley rats (180~200 g) were injected i.m. for 7 or 14 consecutive days with varying doses of aminoglycosides dissolved in physiological saline. On the day after the last treatment, renal function was evaluated by clearance techniques[6]. Each dose group consisted of 6 rats. All values represent mean ±SEM. STUDENT's *t*-test was used for comparison with control values.

Results

The results of broth dilution tests with Sch 21420, gentamicin, tobramycin, and amikacin against a selected group of aminoglycoside-sensitive bacteria, as well as those having defined resistance mechanisms are shown in Table 1. These data show Sch 21420 to have a spectrum of activity and potency essentially the same as that of amikacin. There is a suggestion that Sch 21420 is slightly more potent against several of the *Enterobacteriaceae* while amikacin is slightly more potent against several *Pseudomonas*. Like amikacin, Sch 21420 is active against resistant strains possessing the following enzymes:

(a) Phosphorylating strains, APH (3′)-I and APH (3′)-II

(b) Adenylylating strains, ANT (2″)

(c) Acetylating strains, AAC (3)-I, AAC (3)-II, and AAC (2′).

Also like amikacin, Sch 21420 has reduced activity against the gentamicin sensitive, amikacin-resistant strains which acetylate aminoglycosides at the 6′ amino group, AAC (6′).

To further define the *in vitro* spectrum and potency of Sch 21420 compared to amikacin, gentamicin, and tobramycin, we performed agar dilution MIC determinations for a large number of predominantly resistant recent clinical isolates. Our results with 200 strains of *Pseudomonas aeruginosa* are shown in Table 2. These data confirm the good activity of both amikacin and Sch 21420 against clinically isolated resistant strains.

Similar studies with 152 isolates of other Gram-negative species are shown in Table 3. These data also confirm the broad activity of Sch 21420 against a variety of resistant strains.

Additional *in vitro* tests have shown that Sch 21420, like other aminoglycosides, is bactericidal with MBC values equal to or one dilution higher than MIC values. *In vitro* activity increased with increasing pH and was essentially unaffected by addition of 10% serum to the broth medium. As reported for other aminoglycosides[7], adulteration of media by adding excessive calcium and magnesium increases MIC values particularly for *Pseudomonas*.

Results of comparative mouse protection tests are shown in Table 4 for a selection of Gram-negative bacteria representing for the most part recent clinical isolates. Like amikacin, Sch 21420 had good *in vivo* activity. Both amikacin and Sch 21420 were less active than gentamicin and tobramycin

Table 1. Comparative *in vitro* activity of Sch 21420, gentamicin, tobramycin and amikacin against selected organisms.
Broth dilution MIC's in MUELLER-HINTON broth

Strain		Resistance mechanism	MIC (mcg/ml)			
			Sch 21420	Genta-micin	Tobra-mycin	Amikacin
Bacillus subtilis		Sensitive	0.125	<0.06	<0.06	0.125
Staphylococcus aureus	209P	Sensitive	0.25	<0.06	<0.06	0.25
	Wood	Sensitive	0.5	<0.06	<0.06	0.25
	Ziegler	Sensitive	0.25	0.125	0.125	0.5
Streptococcus	C	Sensitive	>64.0	8.0	16.0	>64.0
	Cruz	Sensitive	>64.0	16.0	16.0	>64.0
	Alvarez	Sensitive	>64.0	16.0	16.0	>64.0
Acinetobacter calcoaceticus	523	Sensitive	8.0	8.0	2.0	8.0
Citrobacter diversus	Charlotte	—	8.0	1.0	2.0	16.0
Citrobacter freundii	Riff 4	—	2.0	2.0	8.0	4.0
	Riff 6	—	2.0	1.0	16.0	8.0
Enterobacter aerogenes	603	Sensitive	1.0	0.25	1.0	1.0
	Charlottesville	ANT (2″)	0.5	8.0	8.0	1.0
Enterobacter cloacae	Birmingham	AAC (3)-I	1.0	64.0	0.5	1.0
Escherichia coli	ATCC 10536	Sensitive	0.25	0.125	0.125	0.5
	St. Michael 589	APH (3′)-I	8.0	2.0	4.0	8.0
	Baker 2	APH (3′)-I	4.0	1.0	2.0	8.0
	W677/R55	ANT (2″)	1.0	64.0	64.0	2.0
	LA290/R55	ANT (2″)	0.5	16.0	16.0	0.5
	JR66	ANT (2″) APH (3′)-I	2.0	64.0	64.0	8.0
	JR 88	AAC (3)-I	1.0	64.0	1.0	2.0
	JR 90	AAC (3)-I	4.0	>64.0	2.0	4.0
	R5/W677	AAC (6′)	16.0	1.0	16.0	32.0
	HL97/W677	AAC (6′)	4.0	0.5	4.0	16.0
	Swidinsky 4195	Unknown	8.0	4.0	32.0	16.0
Flavobacterium sp.	Flo. Ala. 1	Unknown	>128.0	>128.0	>128.0	>128.0
	Flo. Ala. 2	Unknown	>128.0	>128.0	>128.0	>128.0
Klebsiella pneumoniae	AD 17	APH (3′)-II	1.0	0.5	0.25	1.0
	AD 18	APH (3′)-II	0.5	0.25	0.5	2.0
	Georgetown 3694	ANT (2″)	4.0	64.0	32.0	2.0
	Georgetown 3020	ANT (2″)	0.125	16.0	16.0	0.25
Proteus mirabilis	Charlottesville	Sensitive	2.0	0.5	0.5	2.0
Proteus morganii	Garro	Sensitive	0.25	2.0	1.0	0.5
Proteus rettgeri	Membel	Sensitive	0.25	0.5	1.0	0.5
	Anderson	AAC (3)-II	4.0	>64.0	>64.0	1.0
Proteus vulgaris	Napolitano	Sensitive	0.5	0.125	0.125	0.5
	601	AAC (3)-II	2.0	8.0	4.0	1.0
Providencia	164	AAC (2′)	16.0	32.0	16.0	8.0
Pseudomonas aeruginosa	Stone 20	Sensitive	0.25	0.25	0.125	0.25
	Stone 39	Sensitive	1.0	0.25	0.25	1.0
	D-2	APH (3′)	8.0	0.25	0.5	4.0
	Powe	ANT (2″)	1.0	>64.0	16.0	1.0
	Stone 130	AAC (3)-I	1.0	32.0	0.25	0.5
	Stone 138	AAC (3)-I	2.0	>64.0	0.25	1.0
	Travers 1	AAC (3)-II	1.0	>64.0	>64.0	0.5
	GN 315	AAC (6′)-I	64.0	1.0	16.0	16.0
	Shreveport 3796	Unknown	4.0	>64.0	64.0	2.0
	Shriners 10099	Unknown	32.0	32.0	4.0	16.0
	Shriners 10006	Unknown	64.0	16.0	2.0	16.0
Salmonella typhimurium	Group B	Sensitive	4.0	1.0	1.0	4.0
Serratia sp.	Dalton	APH (3′)-I	4.0	1.0	1.0	4.0

Table 2. Comparative *in vitro* activity of Sch 21420, gentamicin, tobramycin and amikacin *versus* recent clinical isolates of *Pseudomonas aeruginosa*. Agar dilution MIC's

Species	Mechanism	N	Anti-biotics*	Cumulative percent susceptible to mcg/ml										
				<0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Pseudomonas	Sensitive	44	21420	—	9	23	31	61	75	90	100			
			GM	9	29	52	75	86	100					
			TM	27	59	84	98	100						
			AMIK	—	5	13	52	68	86	95	100			
	AAC(3)-I	31	21420	—	—	—	13	87	97	97	100			
			GM	—	—	—	—	—	—	6	6	19	30	100
			TM	3	13	16	71	84	94	100				
			AMIK	—	13	19	77	97	97	100				
	AAC(6′)-II	28	21420	—	—	—	18	68	100					
			GM	—	—	—	—	3	7	14	21	43	57	100
			TM	—	—	—	—	—	—	3	46	89	96	100
			AMIK	—	3	7	32	86	100					
	Unknown resistance	97	21420	—	3	7	22	31	55	68	93	100		
			GM	—	2	4	6	18	28	36	38	45	57	100
			TM	—	6	19	38	45	48	52	57	64	84	100
			AMIK	—	—	5	14	47	64	93	98	98	100	

* 21420=Sch 21420, GM=Gentamicin, TM=Tobramycin, AMIK=Amikacin

Table 3. Comparative *in vitro* activity of Sch 21420, gentamicin, tobramycin and amikacin against recent clinical isolates of Gram-negative bacteria

Species	Mechanisms	N	Anti-biotics*	Cumulative percent susceptible to mcg/ml										
				<0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Enterobacter	Sensitive	6	21420	9	27	54	91	100						
	ANT (2″)	4	GM	9	36	46	54	54	54	64	64	82	91	100
	AAC (3)-I	1	TM	9	18	36	46	64	64	73	73	73	82	100
			AMIK	—	9	9	64	100						
E. coli	Sensitive	26	21420	—	19	23	50	62	69	92	100			
			GM	8	42	54	65	92	100					
			TM	12	23	46	50	69	96	100				
			AMIK	—	—	15	38	58	62	88	100			
	ANT (2″)	6	21420	—	—	17	67	83	100					
			GM	—	—	—	—	—	—	50	67	67	100	
			TM	—	—	—	—	—	—	17	67	67	100	
			AMIK	—	—	17	17	67	83	100				
	Others	12	21420	—	—	33	42	58	75	83	92	92	100	
			GM	8	8	8	17	17	33	33	50	67	75	100
			TM	—	—	—	8	17	33	33	42	58	83	100
			AMIK	—	—	—	25	42	67	67	83	92	100	
Klebsiella	Sensitive	11	21420	—	—	36	54	91	100					
			GM	—	18	54	100							
			TM	—	18	45	91	100						
			AMIK	—	—	—	18	91	100					
	ANT (2″)	36	21420	5	22	42	92	97	100					
			GM	—	—	—	—	—	—	14	47	67	86	100
			TM	—	—	—	—	—	—	14	44	69	94	100
			AMIK	—	5	8	69	100						

(to be continued)

Table 3. (continued)

Species	Mechanisms	N	Antibiotics*	Cumulative percent susceptible to mcg/ml										
				<0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Providencia	Sensitive and AAC (2′)	10	21420	—	—	60	70	80	80	80	90	90	100	
			GM	—	—	—	10	20	50	90	90	100		
			TM	—	—	—	10	50	80	80	100			
			AMIK	—	10	50	60	80	80	90	90	100		
Serratia	8 sensitive	40	21420	—	2.5	10	50	67	70	95	100			
	2 ANT (2″)													
	6 AAC (6′)		GM	—	—	13	20	32	35	38	55	60	68	100
	11 AAC (3)-II		TM	—	—	—	10	18	20	25	38	75	90	100
	13 Unknown resistance		AMIK	—	—	2.5	13	60	72	78	98	100		

* 21420=Sch 21420, GM=Gentamicin, TM=Tobramycin, AMIK=Amikacin

Table 4. Comparative *in vivo* activity in mice

Infecting organism		*In vitro* resistance pattern	PD_{50} (mg/kg)			
			Sch 21420	Gentamicin	Tobramycin	Amikacin
Enterobacter	Casey B916	Sensitive	2.0	<0.25	2.5	1.0
	Ridant	Sensitive	0.3	<0.25	<0.25	<0.25
	Jackson	Sensitive	<0.25	<0.25	<0.25	<0.25
	Wiggins	ANT (2″)	10.0	>50.0	>50.0	5.0
Escherichia coli	11775	Sensitive	<0.5	<0.25	0.3	0.3
	627	Sensitive	<0.5	<0.25	<0.25	<0.25
	7112	Sensitive	2.0	0.4	1.5	4.0
	Bold 1	ANT (2″)	40.0	>50.0	>50.0	>50.0
	Engel 3	ANT (2″)	4.0	50.0	>50.0	2.0
Klebsiella pneumoniae	Rosenthal 2	ANT (2″)	0.3	10.0	35.0	1.0
	Brooke Meads	ANT (2″)	1.0	2.0	3.0	1.0
	Brooke McCaig	ANT (2″)	15.0	4.0	1.5	<0.25
	Brooke Espinosa	ANT (2″)	3.0	0.4	0.3	<0.25
Pseudomonas aeruginosa	Cohen Wrig.	Sensitive	<0.5	<0.5	1.0	<0.5
	Carter 2	Sensitive	30.0	<0.5	<0.5	1.0
	Cohen Gold	ANT (2″)	15.0	>50.0	40.0	4.0
	Cohen Ming	ANT (2″)	60.0	>50.0	>50.0	35.0
	Rosen 2	ANT (2″)	15.0	>50.0	35.0	10.0
	Riff 6	ANT (2″)	30.0	>50.0	>50.0	10.0
	Strong M430	ANT (2″)	60.0	35.0	>50.0	35.0
	Cohen McCl	AAC (3)-I	30.0	>50.0	35.0	15.0
	Cohen Dick	AAC (3)-I	4.0	40.0	10.0	3.0
	Cohen Mack	AAC (3)-I	35.0	>50.0	20.0	35.0
	Wat. P179	AAC (3)-I	10.0	35.0	10.0	5.0
	Wat. P183	AAC (3)-I	15.0	40.0	40.0	20.0
Serratia	Brooke 10	Sensitive	15.0	4.0	35.0	10.0
	Brooke 4	Sensitive	<0.25	<0.25	<0.25	<0.25
	Brooke 1	ANT (2″)	0.4	<0.5	0.4	<0.25
	Brooke 3	ANT (2″)	4.0	20.0	35.0	3.0
	Univ. Texas 180	ANT (2″)	20.0	>50.0	>50.0	4.0
	Rosenthal 3	ANT (2″)	15.0	<0.5	4.0	4.0

against gentamicin-sensitive strains but more active against resistant strains.

The acute toxicity of Sch 21420 in mice is shown in Table 5. By the intravenous route, Sch 21420 was approximately four times less toxic than gentamicin. Sch 21420 appears to be only one-tenth as

Table 5. Acute toxicity of Sch 21420 in mice compared with gentamicin

Route	LD_{50} (mg/kg)	
	Sch 21420	Gentamicin
i.v.	330	75
i.p.	~5,000	430
s.c.	~5,000	485

acutely toxic as gentamicin when given subcutaneously or intraperitoneally to mice.

Serum and urine level determinations in groups of mice show that Sch 21420 behaves like other aminoglycosides (Table 6). Peak serum levels were observed within 15 minutes after dosing. Antibiotic levels disappeared rapidly from the serum so that activity was gone from the serum within two hours. The magnitude and duration of these levels are similar to that seen with gentamicin and other aminoglycosides. The serum data can be fit by a single compartment model with serum half-lives ranging between 15 and 23 minutes corresponding to elimination rate constants of $0.045 \sim 0.030$ min^{-1}. Urine obtained at the time of sacrifice showed initially high levels which decline rapidly.

Studies in rats showed a similar pattern. Serum half-lives were approximately 40 minutes corresponding to elimination rate constants of approximately 0.017 min^{-1}.

Results of serum level determinations in dogs are shown in Table 7 after a single bolus i.v. dose of approximately 10 mg/kg. The serum levels were easily fit by a single compartment open model. Serum half-lives were $69 \sim 84$ minutes corresponding to elimination constants of $0.008 \sim 0.01$ min^{-1}. The apparent volume of distribution was found to be $460 \sim 490$ ml/kg.

Sch 21420 was evaluated for effect on renal function in comparison to gentamicin and amikacin.

At a dosage of 80 mg/kg, in single or two divided doses for 7 days (total dose, 560 mg/kg), gentamicin produced glucosuria, a sign of proximal tubular injury (Table 8). In comparison, glucosuria was noted sporadically with amikacin and Sch 21420 at 4 and 8 times the dose of gentamicin, respectively.

The effects of gentamicin, amikacin and Sch 21420 on glomerular filtration rate (GFR) are sum-

Table 6. Serum and urine levels (mcg/ml) of Sch 21420 in mice following a single s.c. dose

	Dose, mg/kg	Time, hours after dosing						
		1/4	1/2	1	1 1/2	2	3	4
Serum levels (mcg/ml)	50	50.0	44.0	6.0	2.2	0.0	0.0	0.0
	25	21.0	15.0	4.0	2.6	0.0	0.0	0.0
	5	9.0	5.0	1.0	1.0	0.0	0.0	0.0
Urine levels (mcg/ml)	50	1,800.0	3,100.0	2,250.0	2,000.0	600.0	200.0	80.0
	25	1,100.0	2,000.0	4,000.0	700.0	400.0	80.0	15.0
	5	200.0	800.0	500.0	700.0	60.0	6.0	3.0

Table 7. Serum levels of Sch 21420 in male beagle dogs following a single i.v. bolus dose of 100 mg (~10 mg/kg)

Dog. No.	Serum levels (mcg/ml) at time, hours after dosing											
	1/12	1/6	1/3	1/2	3/4	1	1 1/2	2	3	4	5	6
BR 35	19.5	30.0	15.0	16.0	11.0	11.5	9.5	5.5	3.5	2.0	1.0	0.0
AD 35	21.0	19.0	22.0	14.5	14.0	12.0	9.0	6.0	3.5	2.5	1.5	1.5

Table 8. Mean arterial blood pressure and incidence of glucosuria in control and aminoglycoside-treated rats

Compound	Treatment[a]	No. of rats	BP (mmHg)[b]	Glucosuria[c]
Saline	0.2 ml/rat o.d. ×7 days	6	118±7	0/6
	0.2 ml/rat o.d. ×14 days	6	133±9	0/6
	0.2 ml/rat b.i.d. ×7 days	24[f]	115±3	1/24
Gentamicin	80 mg/kg o.d. ×7 days	6	107±7	1/6
	120 mg/kg o.d. ×7 days	6	117±10	4/5
	160 mg/kg o.d. ×7 days	6[d]	100±10	3/5
	40 mg/kg b.i.d. ×7 days	6[e]	106±8	3/6
	50 mg/kg b.i.d. ×7 days	6	107±9	3/6
	60 mg/kg b.i.d. ×7 days	12[f]	119±5	6/12
Amikacin	160 mg/kg o.d. ×7 days	6	117±10	0/6
	160 mg/kg o.d. ×14 days	6	130±7	3/6
	80 mg/kg b.i.d. ×7 days	6	105±8	0/6
	125 mg/kg b.i.d. ×7 days	6	98±6*	0/6
	170 mg/kg b.i.d. ×7 days	6	109±8	1/6
	200 mg/kg b.i.d. ×7 days	6	110±4	3/6
	250 mg/kg b.i.d. ×7 days	6	79±6*	1/6
Sch 21420	160 mg/kg o.d. ×14 days	6	117±9	0/6
	320 mg/kg b.i.d. ×7 days	6	89±2*	0/6
	480 mg/kg b.i.d. ×7 days	6	88±2*	0/6
	600 mg/kg b.i.d. ×7 days	6	96±6*	1/6
	640 mg/kg b.i.d. ×7 days	6	77±11*	1/6

[a] The drugs were administered i.m. in saline in a volume similar to that of controls. (o.d.=once daily; b.i.d.=twice daily).

[b] All values represent mean ± standard error. (*) indicates significant difference ($P<0.05$) from appropriate controls.

[c] Glucosuria determined prior to clearance experiments. Numbers signify number of incidences per number of observations. Part of the data in saline control and gentamicin was previously reported (CHIU *et al.*, 1977).

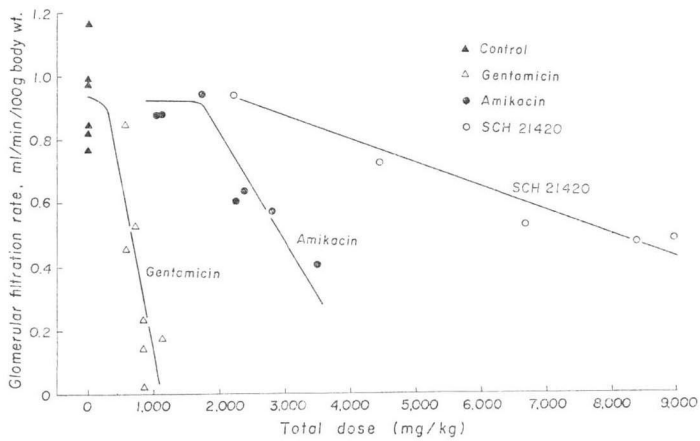
[d] Two rats died during clearance measurement.

[e] One rat died during clearance measurement.

[f] Four and two groups, respectively, of 6 rats each were lumped together because of identical treatment and results.

Fig. 1. Comparison of chronic effect of gentamicin, amikacin and Sch 21420 on glomerular filtration (GFR) in rats.

On the abscissa, is the total amount of drug in mg/kg body weight given to the animals over a period of 7 or 14 days (refer to the table for details). Each point represents the mean value of individual groups consisting of 5 or 6 animals except one gentamicin group of 3 animals. Part of the control and gentamicin data has been describes previously (CHIU *et al.*, 1977).



marized in Fig. 1. All three drugs caused a dose-dependent decline in GFR. On the basis of dose-response curves, a 50% reduction in GFR occurred at a 640 mg/kg total dose of gentamicin compared with 2,920 mg/kg for amikacin and 8,000 mg/kg for Sch 21420. However, it is to be noted that the slope of the dose-response curves varied with individual compounds; gentamicin had the steepest curve, followed by amikacin, and then by Sch 21420.

Gentamicin caused reductions in GFR without affecting mean arterial blood pressure (Table 8). Large doses of amikacin and even greater doses of Sch 21420 yielded hypotensive episodes. While low blood pressure could play a role in impairment of kidney function, there was no correlation between decrease in GFR and hypotension by these drugs.

The results of these chronic renal studies thus demonstrate that Sch 21420 required approximately 4 times the dose of amikacin and 12 times that of gentamicin to produce a 50% reduction in glomerular filtration in rats. Sch 21420 exhibited significant superiority over gentamicin and amikacin in regard to nephrotoxic potential in rats.

Discussion

Sch 21420 has been compared with gentamicin, amikacin and tobramycin in a variety of tests. *In vitro* sensitivity tests, as well as mouse protection tests show that Sch 21420 had a potency and a spectrum similar to those of amikacin. Sch 21420 is active against organisms which adenylate gentamicin and also those which phosphorylate neomycin or kanamycin. In addition, it is active against those organisms which acetylate gentamicin at the 3-N or 2′-N position but not those which acetylate kanamycin at the 6′-N position. Sch 21420 like amikacin was active against a large number of clinical isolates including many *Pseudomonas* and other Gram-negative bacteria which were resistant to gentamicin and tobramycin.

The acute toxicity in mice of Sch 21420 by the i.v. route was significantly lower than that of gentamicin and markedly lower by the s.c. or i.p. routes.

Serum and urine levels of Sch 21420 in mice and rats following s.c. administration at three dose levels were similar to those previously seen with gentamicin at these doses. Half-lives in mouse serum ranged from 15 to 23 minutes while those in rats were 40 minutes.

Pharmacokinetic studies in dogs also showed Sch 21420 to be similar to other aminoglycosides.

The most dramatic difference between Sch 21420 and amikacin was apparent in chronic renal function tests in rats in which Sch 21420 was shown to be only one-fourth as toxic as amikacin.

In summary, Sch 21420 has an *in vitro* and *in vivo* potency and spectrum essentially the same as amikacin with markedly reduced nephrotoxic potential. Further studies to define the toxicological profile of Sch 21420 are underway.

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