ABSORPTION, DISTRIBUTION AND EXCRETION OF SCE-963, A NEW BROAD-SPECTRUM CEPHALOSPORIN, IN MICE, RATS, RABBITS AND DOGS

KANJI TSUCHIYA, MASAHIRO KONDO, YASUO KITA, YUMIKO NOJI, MARIKO TAKEUCHI and TAKESHI FUGONO

Central Research Division, Takeda Chemical Industries, Ltd., Osaka, Japan

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A single dose of 20 mg/kg of SCE-963 [7β-[2-(aminothiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thio]methyl]ceph-3-em-4-carboxylic acid] was administered subcutaneously to mice, intramuscularly to rats, rabbits and dogs. Plasma and tissue levels of SCE-963 reached a peak in 15~30 minutes after administration. In mice, rats and dogs, SCE-963 was distributed at high concentration in the descending order in the kidney, liver, plasma, lung and spleen, and in rabbits, in the kidney, plasma, lung, liver and spleen. The SCE-963 levels in the liver of mice, rats and dogs were higher than those of cefazolin, cephaloridine and cephalothin. The plasma and tissue levels of SCE-963 in mice and rats diminished rapidly, but those in rabbits and dogs declined gradually. SCE-963 was mainly excreted in the urine. The rate of excretion of SCE-963 in the bile was two to three times higher than that of cefazolin.

SCE-963 [7β-[2-(aminothiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thio]methyl]ceph-3-em-4-carboxylic acid], a new broad-spectrum cephalosporin, has a potent *in vitro* and *in vivo* antibacterial activity against Gram-positive and Gram-negative bacteria. The activity of SCE-963 against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* was about 10 times more active than cefazolin, cephaloridine and cephalothin, and against indole-positive *Proteus, Citrobacter freundii* and *Enterobacter cloacae* which have low susceptibility to the cephalosporins, SCE-963 has a potent activity with an inoculum size of 10^6 colony-forming units per ml. The activity of SCE-963 against *Haemophilus influenzae* was similar to that of ampicillin. Furthermore, SCE-963 has an excellent protective activity on mice infected intraperitoneally with several Gram-positive and Gram-negative bacteria[1].

Therefore, it is imperative to conduct a comparative study on plasma levels, tissue distribution, and urinary and biliary excretion of SCE-963, cefazolin, cephaloridine and cephalothin in several species of experimental animals.

Materials and Methods

Cephalosporins.

SCE-963 was prepared in Takeda Chemical Industries, Ltd. Cefazolin (Cefamezin; Fujisawa Pharmaceutical Co., Ltd., Osaka), cephaloridine (Keflodin; Shionogi & Co., Ltd., Osaka) and cephalothin (Keflin; Shionogi & Co., Ltd., Osaka) were obtained from commercial sources. A single dose of 20 mg/kg of cephalosporin dissolved in saline was administered subcutaneously to mice (2 mg/ml, 0.1 ml/10 g), and intramuscularly to rats (10 mg/ml, 0.2 ml/100 g), rabbits (20 mg/ml, 1 ml/kg), and dogs (100 mg/ml, 0.2 ml/kg).

Animals.

Five-week-old male Slc: ICR mice weighing 25~30 g, 7-week-old male JCL: Sprague-Dawley rats weighing 180~250 g, male hybrid rabbits weighing 2.5~3.5 kg, male and female mongrel dogs weighing 9~12 kg, and female beagle dogs weighing 8~10 kg were used.

Specimens for Cephalosporin Assay

Blood samples were collected from *aorta* and *vena axillaris* in mice and rats anesthetized with ethyl ether, from *aorta femoralis* in unanesthetized rabbits and in dogs anesthetized with sodium pentobarbital (Nembutal, Abbot Labs.), and without anesthesia. Blood samples were collected consecutively from the heart in rabbits and from *vena saphena* or *vena medicura* in dogs. Plasma was separated by centrifugation from the heparinized blood sample. After animals were sacrificed by bleeding, lung, liver, spleen, kidney and brain were removed. A small portion of each tissue was homogenized with 2~9-volume of the medium. The medium used was 1/10 M phosphate buffer pH 7 for SCE-963, cefazolin and cephaloridine, and methanol for cephalothin[2]. The homogenate was centrifuged and the supernatant was assayed. Urine samples were collected in metabolism cage from mice and rats, and with an urethral catheter from anesthetized bile-duct cannulated rats, rabbits and dogs. Bile samples were collected from the common bile duct cannulated with polyethylene tubing in rats, rabbits and dogs anesthetized with sodium pentobarbital. In dogs, cystic bile duct was also ligated. All samples were stored at −20°C, and assayed within 7 days after the collection. The cephalosporin activity was stable under these conditions. High recovery rates of cephalosporins from each tissue homogenate were obtained by the test with tissue homogenates containing the final concentration of 20 μg/ml of cephalosporin.

Cephalosporin Assay

The SCE-963 concentration of each specimen was assayed using the cylinder plate diffusion technique with *Proteus mirabilis* ATCC 21100 as a test organism and DST agar (Oxoid) pH 8[3]. The concentration of cefazolin and cephaloridine of each specimen and the cephalothin concentration of plasma, urine, and bile specimens were assayed using the cylinder plate diffusion technique with *Bacillus subtilis* ATCC 6633 as a test organism and sulbenicillin assay medium pH 6.5[4]. The cephalothin concentration in the supernatant of the tissue homogenate was assayed by the paper disk technique. Cephalosporin concentration in plasma was calculated from the standard curve of the cephalopsorin dissolved in plasma. Urine and bile samples were diluted with 1/10 M phosphate buffer pH 7. Cephalosporin activity in urine and bile was not affected by diluting the specimens more than 5 times. Cephalosporin concentration in the diluted specimens and supernatant of the tissue homogenates was calculated from the standard curve of cephalosporin dissolved in 1/10 M phosphate buffer pH 7. The lowest detectable concentration in a sample was 0.1 μg/ml for SCE-963 and cefazolin, 0.05 μg/ml for cephaloridine, and 0.2 μg/ml for cephalothin.

Results

Mice

The peak levels of SCE-963 in plasma and tissues were obtained 15 minutes after administration, and they declined rapidly. SCE-963 distributed at high concentrations in the descending order in the kidney, liver, plasma, lung and spleen, but was absent in the brain. The peak level of SCE-963 in plasma was lower than that of cefazolin and cephaloridine, and higher than that of cephalothin. The plasma levels of these cephalosporins sharply diminished 4 hours after administration. The SCE-963 level in the liver was much higher than those of the reference cephalosporins, and the hepatic levels of the reference cephalosporins were lower than the plasma levels. The SCE-963 level in the kidney was similar to that of cefazolin and cephaloridine, and higher than that of cephalothin (Table 1).

The mean value of urinary excretions of SCE-963 was lower than that of cefazolin and cephaloridine, and higher than that of cephalothin (Table 2).

Rats

The plasma and tissue levels of SCE-963 reached the peak 15 minutes after administration and thereafter the levels declined rapidly. SCE-963 distributed at high concentrations in the descending order in the kidney, liver, plasma, lung and spleen, but was not detected in the brain. The SCE-963 peak level

Table 1. Plasma and tissue levels of SCE-963 and other cephalosporins after a single subcutaneous dose of 20 mg/kg in mice

Cephalosporin	Tissue	Concentration in μg/ml or g (mean±S.D.)				
		1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.
SCE-963 (n=6)	Plasma	12.8±4.3	7.1±1.6	1.5±0.3	0.2	0
	Lung	6.6±2.3	2.6±0.6	0	0	0
	Liver	39.8±10.8	34.6±9.6	6.2±3.1	0	0
	Spleen	0.8	0	0	0	0
	Kidney	65.3±18.6	49.4±4.2	21.3±5.0	2.7	0
	Brain	0	0	0	0	0
Cefazolin (n=5)	Plasma	41.3±11.3	29.0±10.4	8.4±3.9	0.4	0
	Lung	7.6±0.8	5.6±1.7	0	0	0
	Liver	7.7±3.4	5.9±4.3	0	0	0
	Spleen	0	0	0	0	0
	Kidney	63.0±18.4	42.2±15.4	10.7±4.3	0	0
	Brain	0	0	0	0	0
Cephaloridine (n=5)	Plasma	25.5±5.1	14.3±1.3	3.5±0.8	0.3	0
	Lung	11.4±3.8	7.0±2.6	1.4±0.7	0	0
	Liver	11.4±2.7	12.6±2.9	4.0±0.9	0	0
	Spleen	4.1±1.8	2.3±1.2	0	0	0
	Kidney	56.2±12.4	59.4±26.6	12.0±5.1	1.5	0
	Brain	0	0	0	0	0
Cephalothin (n=6)	Plasma	11.5±2.5	4.9±2.3	0.9±0.5	0	0
	Lung	0	0	0	0	0
	Liver	0	0	0	0	0
	Spleen	0	0	0	0	0
	Kidney	14.9±7.2	8.7±4.4	0	0	0
	Brain	0	0	0	0	0

Table 2. Urinary levels and excretion of SCE-963 and other cephalosporins after a single subcutaneous dose of 20 mg/kg in mice

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=10)	0~ 8	277 ± 98.7	47.4± 6.5	Cephaloridine (n=9)	0~ 8	718 ±427	64.6±13.4
	8~24	3.8± 2.9	1.6± 1.1		8~24	16.0± 15.0	6.1± 5.2
	Total		49.0± 6.6		Total		71.0±10.6
Cefazolin (n=7)	0~ 8	760 ±327	59.7±10.4	Cephalothin (n=10)	0~ 8	143 ± 42.8	28.9± 3.3
	8~24	25.8± 19.6	8.9± 5.8		8~24	2.3	1.0
	Total		68.7±10.0		Total		29.9± 2.7

in the plasma was lower than that of the reference cephalosporins. The SCE-963 levels in the kidney and liver were higher than those of the reference cephalosporins, and especially the hepatic level of SCE-963 was higher than that of cefazolin, cephaloridine and cephalothin. For the reference cephalosporins, the levels in the liver were lower than that in the plasma (Table 3).

Table 3. Plasma and tissue levels of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in rats

Cephalosporin	Tissue	Concentration in μg/ml or g (Mean±S.D.)				
		1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.
SCE-963 (n=6)	Plasma	14.6±2.6	8.8±1.3	3.9±0.5	0.2±0.1	0
	Lung	7.7±0.7	4.8±1.3	1.3±0.3	0	0
	Liver	28.4±5.3	24.1±4.8	8.8±1.2	0	0
	Spleen	1.3±0.2	1.0±0.3	0	0	0
	Kidney	91.3±12.4	69.2±20.8	37.6±7.4	3.6±1.6	0
	Brain	0	0	0	0	0
Cefazolin (n=3)	Plasma	44.5±2.9	45.6±2.0	31.9±3.9	7.5±1.0	0
	Lung	16.9±1.3	16.8±1.3	9.6±0.4	4.6±0.3	0
	Liver	20.5±3.0	19.5±4.5	11.3±3.1	3.3±1.1	0
	Spleen	4.2±1.1	4.0±0.5	2.0±0.1	0	0
	Kidney	71.1±15.3	83.3±12.4	54.0±7.0	16.5±0.2	2.2±0.5
	Brain	0	0	0	0	0
Cephaloridine (n=3)	Plasma	26.3±4.5	25.7±5.7	13.4±1.0	1.9±0.7	0.1±0.02
	Lung	7.2±1.6	7.5±1.7	4.7±0.4	1.2±0.3	0.4±0.03
	Liver	3.4±0.9	6.0±1.1	2.0±0.3	0	0
	Spleen	2.1±0.8	2.7±0.6	2.1±0.2	0.6±0.2	0.2±0.01
	Kidney	73.5±24.3	91.6±10.4	49.5±5.4	5.9±1.9	0.5±0.2
	Brain	0	0	0	0	0
Cephalothin (n=3)	Plasma	19.2±1.9	11.7±1.7	2.7±0.7	0	0
	Lung	1.2±0.4	0.9±0.2	0	0	0
	Liver	1.7±1.0	1.5±0.1	0	0	0
	Spleen	0	0	0	0	0
	Kidney	21.3±9.6	10.0±1.8	4.5±1.2	0	0
	Brain	0	0	0	0	0

Table 4. Urinary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in rats

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=5)	0~ 8	316 ± 65.5	42.6± 9.8	Cephaloridine (n=8)	0~ 8	1090 ±152	73.1±10.9
	8~24	13.1± 8.5	3.4± 1.9		8~24	4.6± 2.2	1.1± 0.5
	Total		46.0± 8.1		Total		74.2±10.8
Cefazolin (n=7)	0~ 8	1540 ±501	71.9± 7.0	Cephalothin (n=8)	0~ 8	476 ± 97.5	31.0± 7.6
	8~24	49.4± 27.5	7.7± 4.9		8~24	5.8± 7.3	1.1± 1.0
	Total		79.6± 4.3		Total		32.1± 8.2

The mean value of urinary excretions of SCE-963 was lower than that of cefazolin and cephaloridine, and higher than that of cephalothin (Table 4). In anesthetized bile-duct cannulated rats, the mean values of urinary excretions of 4 cephalosporins were similar to those in unanesthetized rats (Table 5). In bile-duct ligated rats, the mean value of urinary excretions of SCE-963 was 85.8±6.1% of the given

Table 5. Urinary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated rats

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=6)	0~ 2	3,500 ±1,160	19.8±10.1	Cephaloridine (n=3)	0~ 2	3,640 ±1,900	38.1± 7.6
	2~ 4	3,090 ±1,730	23.1± 8.1		2~ 4	3,770 ±1,260	33.2± 5.4
	4~ 6	1,080 ± 622	6.2± 2.6		4~ 6	1,000 ± 290	5.7± 0.5
	6~ 8	383 ± 306	2.4± 1.4		6~ 8	436 ± 379	3.8± 2.9
	8~24	35.5± 23.7	1.5± 0.8		8~24	19.3± 17.0	1.2± 1.1
	Total		53.0± 5.8		Total		82.0± 8.4
Cefazolin (n=3)	0~ 2	4,200 ± 597	47.8± 6.4	Cephalothin (n=6)	0~ 2	1,530 ± 562	12.1± 5.0
	2~ 4	3,060 ± 383	21.4± 8.9		2~ 4	945 ± 271	6.3± 2.6
	4~ 6	1,240 ± 425	5.6± 2.8		4~ 6	185 ± 139	1.8± 1.2
	6~ 8	479 ± 79.0	5.5± 0.7		6~ 8	45.0± 19.1	0.3± 0.2
	8~24	39.8± 12.6	2.7± 0.8		8~24	1.6± 1.7	0.1± 0.1
	Total		83.0± 4.9		Total		20.6± 3.7

Table 6. Biliary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated rats

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=6)	0~ 2	828 ±110	21.8 ±4.3	Cephaloridine (n=3)	0~ 2	5.1±1.0	0.24±0.09
	2~ 4	334 ±140	8.0 ±2.1		2~ 4	6.9±2.0	0.26±0.04
	4~ 6	93.3± 43.1	2.0 ±0.6		4~ 6	2.8±1.2	0.09±0.04
	6~ 8	32.0± 11.8	0.6 ±0.2		6~ 8	0.9±0.5	0.02±0.01
	8~24	4.2± 2.8	0.5 ±0.3		8~24	0.1±0.1	0.01±0.01
	Total		32.9 ±2.6		Total		0.62±0.07
Cefazolin (n=3)	0~ 2	262 ± 49.0	7.6 ±0.3	Cephalothin (n=6)	0~ 2	12.1±3.3	0.37±0.09
	2~ 4	106 ± 43.6	3.1 ±0.8		2~ 4	2.3±1.1	0.06±0.02
	4~ 6	45.9± 38.1	0.7 ±0.4		4~ 6	0.3±0.1	0.01±0.01
	6~ 8	13.9± 10.6	0.3 ±0.2		6~ 8	0	0
	8~24	0.6± 0.7	0.1 ±0.1		8~24	0	0
	Total		11.8 ±1.8		Total		0.44±0.03

dose within 24 hours after administration, which is similar to that of cefazolin and cephaloridine in intact rats. The mean value of biliar excretions of SCE-963 was higher than cefazolin, cephaloridine and cephalothin. Mean biliary levels of SCE-963 at 0~4 hours and 4~8 hours were respectively about 3 times and twice those of cefazolin (Table 6).

Rabbits

The peak levels of SCE-963 in plasma and tissues were obtained 30 minutes after administration. SCE-963 was distributed at high concentrations in the descending order in the kidney, plasma, lung, liver and spleen, but the cephalosporin was not found in the brain. The SCE-963 peak level in the plasma

Table 7. Plasma and tissue levels of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in rabbits

Cephalosporin	Tissue	Concentration in μg/ml or g (Mean±S.D.)					
		1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.
SCE-963 (n=3)	Plasma	25.9±10.4	27.3± 6.8	16.9± 3.0	6.1± 2.4	1.1±0.5	0.3±0.2
	Lung	7.6± 3.1	9.9± 3.3	4.7± 0.8	1.4± 0.4	0	0
	Liver	5.1± 2.2	5.3± 2.6	2.1± 0.6	0	0	0
	Spleen	3.8± 2.3	5.2± 2.1	1.7± 0.6	0	0	0
	Kidney	95.7±12.6	117 ±31.1	58.6± 4.9	30.2±16.8	12.3±3.5	3.2±2.1
	Brain	0	0	0	0	0	0
Cefazolin (n=3)	Plasma	55.2± 9.9	54.0± 2.0	45.1± 3.7	16.8± 4.3	7.6±6.6	0
	Lung	8.5± 3.1	10.0± 1.3	7.1± 0.9	3.2± 1.1	2.1±0.6	1.4±0.5
	Liver	3.0± 1.6	5.3± 1.8	2.1± 0.9	1.0± 0.1	0	0
	Spleen	5.0± 1.2	3.7± 0.4	3.2± 1.1	3.1± 0.6	2.2±0.6	2.0±0.2
	Kidney	139 ±43.4	179 ±83.2	130 ±50.9	41.8± 9.7	10.9±9.2	7.9±7.3
	Brain	0	0	0	0	0	0
Cephaloridine (n=3)	Plasma	32.3±14.7	34.2± 6.9	23.8± 5.9	10.6± 1.0	2.6±0.6	1.3±0.6
	Lung	5.6± 3.1	5.8± 0.5	4.8± 1.7	3.2± 0.9	1.2±0.3	0.5±0.2
	Liver	3.6± 1.8	6.1± 0.4	5.8± 0.9	4.1± 1.0	0.5±0.1	0.3±0.1
	Spleen	2.7± 1.1	2.9± 0.5	3.6± 0.9	1.9± 0.2	1.1±0.1	0.5±0.1
	Kidney	136 ±92.6	217 ± 8.0	226 ±13.4	111 ± 6.2	28.0±4.7	8.6±3.0
	Brain	0	0	0	0	0	0
Cephalothin (n=3)	Plasma	38.6± 4.2	21.3± 8.9	14.3± 5.2	5.4± 4.4	0	0
	Lung	2.2± 0.7	1.3± 0.4	0.6± 0.1	0	0	0
	Liver	2.1± 0.7	1.5± 0.6	0.7± 0.1	0	0	0
	Spleen	1.1± 0.5	0	0	0	0	0
	Kidney	86.8±24.3	58.4±24.3	38.9±12.1	6.4± 4.9	3.3±3.1	0
	Brain	0	0	0	0	0	0

0=Not detected

Table 8. Urinary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in rabbits

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=5)	0~ 2	2,130 ±1,440	30.7±12.9	Cephaloridine (n=3)	0~ 2	1,160 ± 534	17.3± 4.6
	2~ 4	1,400 ±1,350	38.8± 9.2		2~ 4	2,010 ±1,250	25.7± 9.2
	4~ 6	830 ± 457	10.1± 3.5		4~ 6	1,280 ± 578	6.7± 3.7
	6~ 8	440 ± 199	5.7± 2.5		6~ 8	460 ± 176	3.7± 1.7
	8~24	46.3± 18.3	3.7± 1.4		8~24	30.8± 9.3	2.1± 0.1
	Total		89.0± 4.8		Total		55.5±12.7
Cefazolin (n=3)	0~ 2	2,520 ± 790	48.1±14.3	Cephalothin (n=3)	0~ 2	851 ± 324	22.4± 3.8
	2~ 4	489 ± 249	27.3±10.0		2~ 4	200 ± 124	3.7± 2.2
	4~ 6	430 ± 191	7.4± 3.4		4~ 6	227 ± 91.1	2.1± 0.8
	6~ 8	349 ± 80.9	2.8± 0.6		6~ 8	111 ± 78.9	1.3± 0.8
	8~24	56.3± 49.9	2.3± 0.6		8~24	11.4± 12.3	0.7± 0.6
	Total		87.9± 3.4		Total		30.2± 2.4

was lower than that of the reference cephalosporins, and the SCE-963 peak level in the kidney was lower than that of cefazolin and cephaloridine, and higher than that of cephalothin (Table 7).

The mean value of urinary excretions of SCE-963 was similar to that of cefazolin, and higher than that of cephaloridine and cephalothin (Table 8). In anesthetized bile-duct cannulated rabbits, the mean values of urinary excretions of four cephalosporins were similar to those in unanesthetized rabbits, but the excretion rates in the former was slower than that in the latter (Table 9). The mean value of biliary excretions of SCE-963 was higher than that of cefazolin, cephaloridine and cephalothin, but biliary excretions of 4 cephalosporins in rabbits were much lower than that of other animal species (Table 10).

Table 9. Urinary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated rabbits

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=3)	0~ 2	2,080 ±1,150	16.4± 7.5	Cephaloridine (n=3)	0~ 2	398 ± 321	7.0± 3.2
	2~ 4	4,040 ±1,110	25.0± 9.3		2~ 4	1,720 ±1,550	16.8±11.1
	4~ 6	2,660 ±1,310	15.0± 5.5		4~ 6	1,490 ± 490	7.5± 6.6
	6~ 8	1,120 ± 348	7.2± 3.7		6~ 8	1,280 ± 614	11.1± 3.1
	8~24	239 ± 111	9.6± 4.0		8~24	456 ± 438	11.8± 2.0
	Total		73.2±10.4		Total		54.2± 9.8
Cefazolin (n=3)	0~ 2	1,540 ±1,470	14.0± 8.2	Cephalothin (n=3)	0~ 2	747 ± 599	12.9± 3.5
	2~ 4	4,150 ±1,610	26.3±12.4		2~ 4	628 ± 490	4.5± 3.5
	4~ 6	3,110 ±1,460	19.0± 3.7		4~ 6	561 ± 471	2.9± 1.8
	6~ 8	1,360 ± 768	10.2± 3.7		6~ 8	245 ± 227	1.6± 1.5
	8~24	342 ± 147	10.8± 5.9		8~24	65.9± 41.5	3.1± 2.3
	Total		80.3±23.9		Total		24.9± 4.8

Table 10. Biliary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated rabbits

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=3)	0~ 2	16.1±6.9	0.51±0.23	Cephaloridine (n=3)	0~ 2	6.2±4.0	0.29±0.20
	2~ 4	17.0±7.9	0.44±0.17		2~ 4	8.4±3.3	0.26±0.17
	4~ 6	9.7±3.8	0.22±0.07		4~ 6	4.8±1.2	0.11±0.04
	6~ 8	6.7±2.0	0.14±0.04		6~ 8	3.9±1.6	0.07±0.04
	8~24	2.0±1.1	0.21±0.10		8~24	1.4±0.7	0.12±0.02
	Total		1.52±0.38		Total		0.85±0.45
Cefazolin (n=3)	0~ 2	8.2±5.2	0.17±0.05	Cephalothin (n=3)	0~ 2	5.2±1.9	0.12±0.02
	2~ 4	9.2±8.7	0.21±0.13		2~ 4	2.7±1.5	0.06±0.02
	4~ 6	4.3±2.3	0.10±0.04		4~ 6	1.0±0.4	0.02±0.002
	6~ 8	3.6±0.8	0.07±0.02		6~ 8	0.5±0.3	0.01±0.004
	8~24	1.2±0.1	0.14±0.01		8~24	0.4±0.3	0.01±0.01
	Total		0.69±0.14		Total		0.22±0.04

Dogs

The peak level of SCE-963 in plasma appeared 30 minutes after administration, and the SCE-963 levels persisted until 8 hours after administration. The peak plasma level of SCE-963 was similar to that of cefazolin, but higher than that of cephaloridine and cephalothin (Table 11). SCE-963 was distributed at high concentrations in the descending order in the kidney, liver, plasma and spleen, but it did not appear in the brain. The SCE-963 level in the liver was higher than the plasma level, and was similar to the renal level (Table 12). When tissue levels of 4 cephalosporins at 30 minutes after administration were compared, the hepatic level of SCE-963 was higher than those of the reference cephalosporins (Table 13).

Table 11. Plasma levels of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in mongrel dogs

Cephalosporin	Concentration in μg/ml (Mean±S.D.)						
	1/4 hr.	1/2 hr.	1 hr.	2 hrs.	4 hrs.	6 hrs.	8 hrs.
SCE-963 (n=3)	33.4± 7.4	43.2± 0.5	28.6±3.2	11.9±2.4	2.5±1.1	0.7±0.4	0.1
Cefazolin (n=4)	40.2± 4.6	41.5± 5.5	37.2±4.1	19.9±2.3	3.7±0.2	0	0
Cephaloridine (n=3)	30.3±14.5	37.5±14.3	31.8±4.5	11.9±0.8	4.0±1.0	0.7±0.3	0.1
Cephalothin (n=3)	19.9± 3.1	17.6± 2.4	12.6±0.9	2.5±0.9	0.2±0.1	0	0

0=Not detected

Table 12. Plasma and tissue levels of SCE-963 after a single intramuscular dose of 20 mg/kg in mongrel dogs

Tissue	Concentration in μg/ml or g (Mean±S.D.)				
	1/2 hr.	1 hr.	2 hrs.	4 hrs.	8 hrs.
Plasma	30.7± 3.2	21.6± 4.2	9.7±2.3	0.6±0.3	0
Lung	13.4± 4.9	8.5± 4.3	2.4±1.1	0	0
Liver	91.5±16.9	52.3±24.2	16.1±9.4	0	0
Spleen	5.0± 1.2	2.5± 0.8	0.6	0	0
Kidney	90.2±27.8	58.1±18.0	25.8±9.1	2.8±0.9	0
Brain	0	0	0	0	0

0=Not detected

Table 13. Plasma and tissue levels of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in mongrel dogs 30 minutes after administration

Tissue	Concentration in μg/ml or g (Mean±S.D.)			
	SCE-963 (n=5)	Cefazolin (n=5)	Cephaloridine (n=5)	Cephalothin (n=5)
Plasma	30.7± 3.2	35.8± 3.6	39.2± 6.6	21.3± 3.5
Lung	13.4± 4.9	14.4± 2.8	18.9± 3.9	5.3± 1.4
Liver	91.5±16.9	18.9±10.1	11.0± 3.3	5.9± 3.2
Spleen	5.0± 1.2	5.8± 0.5	6.0± 1.2	0
Kidney	90.2±27.8	93.3±37.2	128.2±43.1	36.0±11.2
Brain	0	0	0	0

0=Not detected

In anesthetized bile-duct cannulated mongrel dogs, the urinary and biliary excretions of 4 cephalosporins were compared. The urinary and biliary excretions of SCE-963 were also studied in beagle dogs. In anesthetized bile-duct cannulated mongrel dogs, the mean value of urinary excretions of SCE-963 was similar to that of cefazolin and cephaloridine, and higher than that of cephalothin (Table 14).

Table 14. Urinary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated mongrel dogs

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=3)	0~ 2	6,480 ±2,470	49.8± 4.8	Cephaloridine (n=3)	0~ 2	10,700 ±2,020	57.2± 9.9
	2~ 4	2,620 ± 793	19.1± 5.6		2~ 4	4,030 ±1,430	25.0± 3.5
	4~ 6	1,000 ± 125	7.0± 1.4		4~ 6	1,340 ± 904	7.1± 3.5
	Total		75.9± 5.1		Total		89.3± 6.4
Cefazolin (n=3)	0~ 2	6,510 ±2,460	27.1± 6.7	Cephalothin (n=3)	0~ 2	6,690 ± 549	31.8± 0.2
	2~ 4	4,580 ±1,950	19.1± 7.4		2~ 4	1,590 ± 678	8.1± 2.8
	4~ 6	2,940 ±1,930	9.5± 6.6		4~ 6	417 ± 245	2.1± 1.1
	Total		55.7±20.5		Total		41.9± 3.6

Table 15. Biliary levels and excretion of SCE-963 and other cephalosporins after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated mongrel dogs

Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Cephalosporin	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
SCE-963 (n=3)	0~ 1	328 ± 197	0.45±0.30	Cephaloridine (n=3)	0~ 1	8.8± 6.0	0.017±0.010
	1~ 2	1,450 ± 377	1.08±0.51		1~ 2	26.4± 12.8	0.045±0.030
	2~ 4	1,200 ± 583	0.85±0.41		2~ 4	23.3± 8.7	0.058±0.040
	4~ 6	468 ± 388	0.57±0.40		4~ 6	8.4± 3.0	0.017±0.011
	Total		2.95±1.55		Total		0.138±0.108
Cefazolin (n=3)	0~ 1	57 ± 20	0.05±0.03	Cephalothin (n=3)	0~ 1	30.0± 18.6	0.040±0.020
	1~ 2	739 ± 459	0.31±0.03		1~ 2	56.9± 40.7	0.070±0.030
	2~ 4	1,190 ±1,080	0.60±0.37		2~ 4	20.1± 10.3	0.040±0.020
	4~ 6	989 ± 184	0.59±0.40		4~ 6	7.1± 3.4	0.010
	Total		1.55±0.82		Total		0.160±0.060

Table 16. Urinary and biliary levels and excretion of SCE-963 after a single intramuscular dose of 20 mg/kg in anesthetized bile-duct cannulated beagle dogs

Specimen	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)	Specimen	Time (Hour)	Concentration in μg/ml (Mean±S.D.)	Percent excretion (Mean±S.D.)
Urine (n=4)	0~ 2	9,490±1,860	38.0±4.6	Bile (n=4)	0~ 1	1,170± 400	2.6±1.7
	2~ 4	3,660±1,240	17.7±3.5		1~ 2	2,240± 653	4.6±1.8
	4~ 6	1,410± 698	6.8±2.6		2~ 4	1,200± 218	3.4±3.1
	6~ 8	572± 430	2.8±2.0		4~ 6	478± 165	1.2±0.7
					6~ 8	213± 97	0.4±0.1
	Total		65.3±6.5		Total		12.1±3.9

The mean value of biliary excretions of SCE-963 was higher than cefazolin, cephaloridine and cephalothin (Table 15). In beagle dogs, though the mean value of urinary excretions of SCE-963 was similar to that in mongrel dogs, the mean value of biliary excretions of SCE-963 in beagle dogs was higher than that in mongrel dogs. The mean biliary level of SCE-963 in both mongrel and beagle dogs was about the same, though the rate of bile excretion was 1~2 ml per hour in mongrel dogs and 3~4 ml per hour in beagle dogs (Table 16).

Discussion

SCE-963 was absorbed rapidly from the injection site, and the plasma and tissue levels reached the peak in 15~30 minutes after administration. The renal level of SCE-963 was the highest among the tissues which was similar to the findings with cefazolin, cephaloridine and cephalothin. The hepatic level of SCE-963, however, differed considerably from that of the reference cephalosporins, and was higher than the plasma level in mice, rats and dogs. In contrast, the distribution pattern of SCE-963 in rabbits was similar to that of the reference cephalosporins. These results were reflected in the excretion patterns of 4 cephalosporins. Urinary excretion of SCE-963 in rabbits was similar to those of the reference cephalosporins, but in mice, rats and dogs, the urinary excretion was relatively low. SCE-963 was excreted well into the bile. The mean value of biliary excretions of SCE-963 was about 3 times higher than that of cefazolin in rats and dogs, and about twice as high in rabbits. The total biliary excretion was about 3% in mongrel dogs, and about 12% in beagle dogs. However, the biliary levels of SCE-963 in both mongrel and beagle dogs were similar; this appears to be due to the fact that the rate of excretion of the bile in beagles (3~4 ml/hour) was twice to 4 times more than that in mongrel dogs. In rats, about 30% of the given dose of SCE-963 excreted in the bile, and the urinary excretion of SCE-963 was about 50% of the given dose. However, the total excretion of SCE-963 in urine and bile was similar to the urinary excretions of cefazolin and cephaloridine. In addition, in bile duct-ligated rats, the urinary excretion of SCE-963 was similar to that of cefazolin and cephaloridine in intact animals. It is well known that a large amount of a less active metabolite, desacetyl cephalothin, is excreted in the urine of animals which received cephalothin. Therefore, the excretion profile of cephalothin cannot be measured by the simple biological assay method[2]. No active metabolites of SCE-963 were observed in the urine of rats. Accordingly, low urinary excretion of SCE-963 in rats was the results of a high biliary excretion. RYRFELDT[5] indicated that the biliary excretion of penicillins increased in parallel with increase in the polarity of the molecules. A similar tendency was observed in the 4 cephalosporins tested.

In mice, rats and dogs, the pulmonary levels of cephalosporins varied in accordance with the plasma levels. However, the pulmonary levels of SCE-963 were about 50% of the corresponding plasma levels, those of cefazolin were 20~30%, and those of cephaloridine were 25~50%. BARZA *et al.*[6] reported that minocycline, a strong basic tetracycline, showed a high degree of tissue distribution compared with other tetracyclines. WONG *et al.*[7] reported that gentamicin showed a higher ability to enter bronchial secretions than cephalothin and ampicillin did. It is of interest to note that minocycline and gentamicin are both basic compounds among the reference compounds used in these reports.

It should be noted that SCE-963 is a basic compound among the cephalosporins used. Although the level of SCE-963 in the lung does not necessarily reflect the level in the bronchial specimens, SCE-963 may have a potential ability to enter the blood-broncho-alveolar barrier. The secretion of cephalosporins into bronchi and alveoli will require further studies.

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