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Comparative Pharmacokinetics of SCE-2787 and Related Antibiotics in Experimental Animals

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The pharmacokinetic properties of SCE-2787 administered intravenously at a dose of 20 mg/kg of body weight were studied with mice, rats, rabbits, dogs, and monkeys and were compared with those of ceftazidime, cefpirome, and cefclidin in mice and dogs. The area under the concentration-time curve for plasma after intravenous administration was the largest in monkeys, followed by those in dogs, rabbits, rats, and mice, in that order. The elimination half-life ranged from 0.2 to 0.3 h in mice and rats to 0.7 to 1.3 h in rabbits, dogs, and monkeys. In young dogs, the concentrations of SCE-2787 in plasma were somewhat lower than those in the mature dogs. SCE-2787 was distributed well to the tissues, and the highest concentration was found in the kidneys in all species tested; the distribution to the lungs, liver, and spleen was also good, but the concentrations in these tissues were lower than those in the plasma. The pharmacokinetic parameters and urinary excretion of SCE-2787 in mice and dogs were similar to those of ceftazidime, cefpirome, and cefclidin. The maximum concentrations in the cerebrospinal fluid of rats and rabbits were 0.8 and 1.3 μg/ml, and the relative percentages of the area under the concentration-time curve of SCE-2787 in the cerebrospinal fluid to that in the plasma were 4.6 and 6.4%, respectively. SCE-2787 was excreted mainly in the urine; the recovery rate ranged from 74% (rats) to 90% (dogs) of the dose. The biliary excretion of SCE-2787, however, was low, amounting to about 1.4% for mice and rats and less than 0.5% for rabbits and dogs. In rats, there was no accumulation in the tissues and no delay in urinary excretion upon multiple intravenous administration of 20 mg of SCE-2787 per kg once daily for 7 days. No active metabolites were found in the plasma or urine of animals given SCE-2787. The binding of SCE-2787 to serum protein in mice, rats, rabbits, dogs, monkeys, and humans was less than 11% and similar to that of cefclidin.

SCE-2787 (Fig. 1) is a new injectable cephalosporin that has potent and well-balanced antibacterial activity against a wide range of aerobic gram-positive and gram-negative bacteria, such as *Staphylococcus aureus*, members of the family *Enterobacteriaceae*, and *Pseudomonas aeruginosa* (3, 6). Its activity is similar to that of structurally related antibiotics, such as ceftazidime, cefpirome, and cefclidin, but SCE-2787 is more potent than ceftazidime against gram-positive cocci and members of the *Enterobacteriaceae* and comparable to ceftazidime and more potent than cefpirome against *P. aeruginosa*.

In the present study, the pharmacokinetic properties of SCE-2787 in experimental animals were compared with those of ceftazidime, cefpirome, and cefclidin.

(The results of this study were presented in part at the 29th International Congress on Antimicrobial Agents and Chemotherapy, Houston, Tex., in 1989 [12].)

MATERIALS AND METHODS

Antibiotics. SCE-2787, cefpirome, and cefclidin were prepared in the Research and Development Division of Takeda Chemical Industries, Ltd., Osaka, Japan. Ceftazidime was obtained commercially.

Animals. Five-week-old male Slc:ICR mice weighing 20 to 25 g, 7-week-old male Jcl:SD rats weighing 190 to 230 g, 2- to 3-month-old male New Zealand White rabbits weighing 2 to 2.5 kg, 3-week-old male or 7- to 12-month-old male and female Toyo beagle dogs weighing 0.8 to 0.9 or 8 to 13 kg, and male and female cynomolgus monkeys weighing 2.1 to 2.9 kg were used. All animals were fasted for 16 to 18 h before the antibiotic was administered; water was given ad libitum.

Antibiotic administration. Just before use, each antibiotic was dissolved in sterile saline. A single dose of 20 mg of the antibiotic per kg of body weight was administered intravenously to mice (2 mg/ml, 0.1 ml/10 g of body weight), rats (10 mg/ml, 0.2 ml/100 g), rabbits (40 mg/ml, 0.5 ml/kg), dogs (50 mg/ml, 0.4 ml/kg), and monkeys (50 mg/ml, 0.4 ml/kg).

Specimens for antibiotic assay. Blood specimens were collected in heparinized syringes from the axillary artery and vein of mice and rats under anesthesia with ethyl ether, from the carotid artery of rabbits, from the saphenous and median veins of dogs, and from the femoral vein of monkeys. Plasma was separated by centrifugation at 2,000 × *g* for 10 min at 2°C.

Cerebrospinal fluid (CSF) specimens were collected by intracisternal puncture after rats were killed by bleeding and rabbits were anesthetized with sodium pentobarbital (Nembutal; Abbott Laboratories).

After the animals were killed by bleeding, the lungs, liver, kidneys, and spleen were removed and washed with cold saline. The tissues were homogenized with 9 parts (wt/vol) of 0.1 M phosphate buffer (pH 7.0). Each homogenate was centrifuged, and the supernatant was used for the bioassay.

Urine specimens were collected from mice, rats, and monkeys in metabolism cages and from unanesthetized rabbits and dogs with a urethral catheter over fixed intervals. Bile specimens were collected from the common bile duct cannulated with polyethylene tubing under anesthesia with ethyl ether in mice and rats and with sodium pentobarbital in rabbits and dogs over the fixed intervals.

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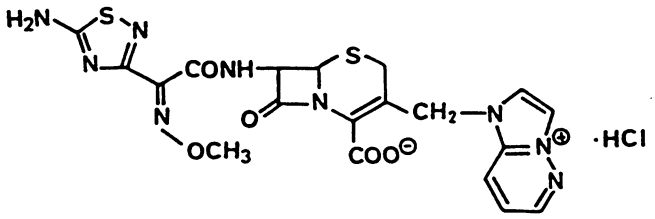

FIG. 1. Chemical structure of SCE-2787.

All specimens were assayed immediately after each experiment or stored at −80°C and assayed within a week. The antibiotics were stable under these conditions.

Antibiotic assays. (i) Microbiological assay. The concentrations of SCE-2787 and related antibiotics in body fluids and tissue extracts were assayed by the agar well method. *Escherichia coli* NIHJ and *Providencia rettgeri* ATCC 9250 were used as the test organisms in assay media, Daigo no. 6 (Nihon Seiyaku Co.) and MacConkey agar (Eiken Chemical Co.), respectively. The sensitivities of the assays were about 0.3 μg/ml (the concentration range of standards with *E. coli*, 20 to 0.3 μg/ml) and 0.03 μg/ml (with *P. rettgeri*, 0.5 to 0.03 μg/ml). The intraday coefficients of variation in the replicate analyses (n = 12) for the standard curves with 0.1 M phosphate buffer (pH 7.0) were ±5.8% (*E. coli*) and ±6.9% (*P. rettgeri*). There was good agreement (correlation coefficient: r = 0.991 to 0.998) between the results obtained by the bioassay and by high-pressure liquid chromatography (unpublished data).

The antibiotic concentrations in plasma were calculated from the calibration curves for the drugs dissolved in normal plasma from the respective animals. Urine and bile specimens were diluted with 0.1 M phosphate buffer (pH 7.0). The antibiotic concentrations in the diluted specimens and the tissue homogenate supernatant were calculated from the calibration curves for the drugs dissolved in the buffer.

(ii) Bioautography of active metabolites. The biologically active metabolites in plasma and urine specimens were determined by thin-layer chromatography–bioautography. Plasma specimens were mixed with 3 volumes of methanol, and the supernatant was separated by centrifugation. Urine specimens were diluted with an appropriate volume of 1 M acetate buffer (pH 5.0). The supernatant, urine, and standard antibiotic solutions were spotted on a thin-layer plate (Spotfilm silica gel; Tokyo Chemical Industry Co., Ltd.). After ascending development in the solvent acetone-acetic acid-water-ammonia water (15:8:4:1, vol/vol), the active spots were detected by bioautography with *P. rettgeri* ATCC 9250 as the test organism on MacConkey agar. The sensitivity of this bioautography was about 0.003 μg of SCE-2787 equivalent.

Protein binding. The degree of protein binding of SCE-2787 and cefclidin in serum was determined by the centrifugal ultrafiltration method (1). To 1.96 ml of the serum from various species of animals was added 0.04 ml of an antibiotic solution (final concentration, 20 μg/ml). The mixture was incubated at 37°C for 10 min and transferred to an MPS-3 type ultrafilter (Amicon Corp.) for centrifugation (1,000 × g, 10 min). The antibiotic concentration in the filtrate was determined by bioassay for the calculation of the degree of protein binding.

Pharmacokinetic analysis. Pharmacokinetic evaluation was performed by using the nonlinear least-squares program (MULTI) reported by Yamaoka et al. (11); the optimum values of parameters for the one- or two-compartment open model were determined by the Akaike information criterion index calculated in this program and by the visual inspection of the dispersion of residual errors. The best model is considered to give the least Akaike information criterion index. All data were weighted with the reciprocal squared concentration.

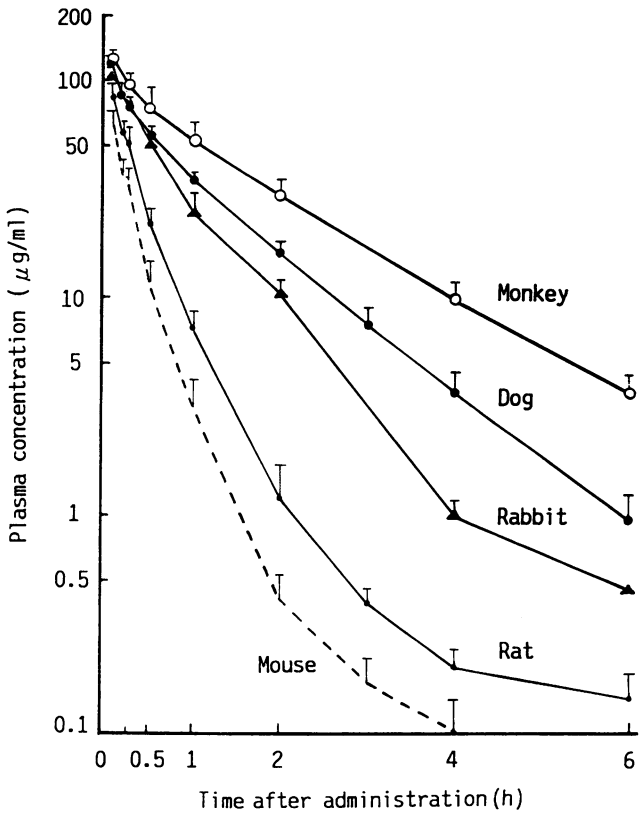

FIG. 2. Concentrations of SCE-2787 in plasma in experimental animals after a single intravenous dose of 20 mg/kg.

The pharmacokinetic parameters for the antibiotic in mice and rats were calculated from the mean levels in plasma by the one-compartment open model, which fit satisfactorily for their calculations; the parameters in rabbits, dogs, and monkeys were calculated by the two-compartment open model, since their elimination-phase curves did not fit the one-compartment open model.

Statistical analysis. The degree of significance between means was determined by the Student t test.

RESULTS

Concentrations in plasma. The concentrations of SCE-2787 in the plasma of mice, rats, rabbits, dogs, and monkeys given a single intravenous dose of 20 mg/kg are shown in Fig. 2. Values for the area under the concentration-time curve for plasma (AUC), the apparent elimination half-life ($t_{1/2}$), the apparent distribution volume (V), and the plasma clearance (CL_P) for SCE-2787 and reference antibiotics are shown in Table 1.

Both the AUC and $t_{1/2}$ were the largest in monkeys, followed by those in dogs, rabbits, rats, and mice, in that order. The V (0.20 to 0.27 liter/kg) was similar in all animal species tested. The CL_P for mice and rats (9 to 15 ml/min/kg)

TABLE 1. Pharmacokinetic parameters of SCE-2787 and reference antibiotics in experimental animals

Antibiotic[a]	Animal (n)	Parameter[b]				Urinary excretion[c] (%)
		AUC (μg · h/ml)	$t_{1/2}$ (h)	V^d (liter/kg)	CL_P (ml/min/kg)	
SCE-2787	Mouse (10)	21.8	0.20	0.27	15.3	85.0
	Rat (10)	35.5	0.25	0.20	9.4	74.4
	Rabbit (3)	84.4	0.73	0.21	4.0	88.6
	Dog (5)	112	0.88	0.21	3.0	89.7
	Young dog (4)	63.4	0.98	0.40	5.3	—
	Monkey (4)	174	1.34	0.20	1.9	82.3
Ceftazidime	Mouse (5)	23.5	0.17	0.18	14.2	77.9
	Dog (5)	105	0.86	0.21	3.2	71.7
	Young dog (4)	52.6	0.87	0.43	6.3	—
Cefpirome	Mouse (5)	20.1	0.19	0.26	16.6	92.8
	Dog (5)	103	0.90	0.22	3.2	82.3
Cefclidin	Mouse (5)	25.3	0.19	0.20	13.2	79.0
	Dog (5)	101	0.87	0.23	3.3	76.3

[a] Antibiotic was intravenously administered at a dose of 20 mg/kg.
[b] Pharmacokinetic parameters were calculated from the mean levels in plasma by the one-compartment open model (mice and rats) or the two-compartment open model (other animals).
[c] Recovery of antibiotic within the first 8 h after administration in dogs and within the first 24 h in other animals. —, not tested.
[d] Expressed as apparent V (for one-compartment open model) and steady-state V (for two-compartment open model).

was higher than that for other animals (2 to 4 ml/min/kg). The pharmacokinetic parameters of ceftazidime, cefpirome, and cefclidin in mice and dogs after the intravenous administration of 20 mg/kg were very similar to those of SCE-2787. The AUC (63.4 μg · h/ml) in young dogs was lower than that in mature dogs, but the $t_{1/2}$ (0.98 h) in young dogs was comparable to that in mature dogs. The pharmacokinetic parameters of SCE-2787 in young dogs were similar to those of ceftazidime.

Distribution in tissue. The concentrations of SCE-2787 in tissues in mice and rats (Table 2) and in rabbits, dogs, and monkeys (Table 3) were determined periodically after a 20-mg/kg dose was administered intravenously. When the concentrations in tissues were compared 15 min after the antibiotic was administered, the distribution patterns were similar for mice, rats, rabbits, and monkeys; the SCE-2787 concentrations were the highest in the kidneys, followed by those in the plasma, lungs, liver, and spleen, in that order. In dogs, the concentration of SCE-2787 was the highest in the kidneys, followed by that in the plasma, liver, lungs, and spleen, in that order.

Concentrations in CSF. The concentrations of SCE-2787 in the plasma and CSF of rats and rabbits given a single intravenous dose of 20 mg/kg are shown in Table 4. The maximum concentrations in the CSF of rats and rabbits were 0.8 and 1.3 μg/ml, respectively. The penetration ratio into the CFS, which was calculated as the percentage of the AUC of SCE-2787 in the CSF relative to the AUC in the plasma, was 4.6% (rats) and 6.4% (rabbits).

Urinary and biliary excretion. (i) Urinary excretion. The concentrations and recovery of SCE-2787 from the urine in five animal species are shown in Table 5. High concentrations of SCE-2787 were found in the urine, and most of the antibiotic was excreted within the first 8 h after administration. The recovery of SCE-2787 in mice, rabbits, dogs, and monkeys exceeded 80% and was similar to that of cefpirome and slightly higher than that of ceftazidime and cefclidin in mice and dogs (Table 1).

(ii) Biliary excretion. The biliary concentrations and recovery of SCE-2787 in mice, rats, rabbits, and dogs are shown in Table 6. The recovery of SCE-2787 within 24 h was generally low, ranging from 0.28 to 1.36%. The biliary concentrations of SCE-2787, however, reached levels which exceed the MIC against most of the aerobic gram-positive and gram-negative bacteria (3).

No conjugated form of SCE-2787 was found in the urine or bile of any animal species: there were no significant changes in the concentration of SCE-2787 in the samples after treatment with a β-glucuronidase and sulfatase preparation partially purified from *Helix pomatia* (Sigma Chemical Co.).

Multiple administration. When SCE-2787 was administered to rats intravenously at a dose of 20 mg/kg once daily for 7 days, the pharmacokinetic parameters (AUC, 35.0 μg · h/ml; $t_{1/2}$, 0.24 h; V, 0.20 liter/kg; CL_P, 9.5 ml/min/kg; urinary recovery, 75.7%) after the seventh dose did not differ significantly from those after the first dose (data not shown).

Active metabolites. Active metabolites of SCE-2787 in the plasma and urine of mice, rats, rabbits, dogs, and monkeys were examined by thin-layer chromatography–bioautography. No active metabolites of SCE-2787 (R_f, 0.48) were detected in any of the plasma or urine samples.

Serum protein binding. The extent of protein binding of SCE-2787, estimated by the centrifugal ultrafiltration method, did not exceed 11% in the sera of any of the experimental animals or humans and was similar to that of cefclidin (Table 7).

DISCUSSION

SCE-2787 is a new cephalosporin derivative characterized by its broad-spectrum antibacterial activity and excellent protective effects against systemic infections caused by a variety of gram-positive and gram-negative bacteria (3, 6). It has been found to exhibit excellent therapeutic effects in models of respiratory and urinary tract infection caused by *Klebsiella pneumoniae* and *P. aeruginosa*, respectively (3, 6). It has also been found to be of good therapeutic value in clinical trials (unpublished data).

TABLE 2. Concentrations of SCE-2787[a] in plasma and tissues of mice and rats

Animal	Plasma or tissue	Concn (μg/ml or μg/g)[b] after:							
		1/12 h	1/6 h	1/4 h	1/2 h	1 h	2 h	3 h	4 h	6 h
Mouse	Plasma	61.4 ± 10.0	36.8 ± 5.2	34.5 ± 4.9	12.2 ± 2.3	3.2 ± 1.0	0.41 ± 0.12	0.17 ± 0.05	0.10 ± 0.04	ND
	Lung	18.1 ± 6.5	12.9 ± 2.0	11.3 ± 1.9	4.7 ± 1.1	2.4 ± 0.7	1.0 ± 0.2	0.7 ± 0.1	0.4 ± 0.2	ND
	Liver	9.1 ± 0.9	8.8 ± 1.3	8.3 ± 1.7	6.9 ± 1.7	4.9 ± 0.9	2.8 ± 0.5	1.6 ± 0.3	1.3 ± 0.3	0.9 ± 0.4
	Kidney	80.2 ± 22.0	50.3 ± 16.0	37.7 ± 17.6	21.1 ± 9.3	4.4 ± 1.1	1.0 ± 0.5	0.7 ± 0.5	0.3 ± 0.3	0.4 ± 0.4
	Spleen	5.8 ± 1.1	6.3 ± 4.1	5.3 ± 1.3	3.0 ± 1.2	2.0 ± 2.1	1.7 ± 0.6	1.3 ± 0.3	1.3 ± 0.8	0.7 ± 0.4
Rat	Plasma	84.3 ± 11.9	56.8 ± 7.7	52.1 ± 9.8	21.6 ± 3.6	7.4 ± 1.1	1.2 ± 0.5	0.39 ± 0.06	0.20 ± 0.04	0.14 ± 0.04
	Lung	30.6 ± 2.1	23.7 ± 3.1	20.5 ± 4.3	9.2 ± 1.2	4.6 ± 1.0	1.4 ± 0.2	0.7 ± 0.1	0.3 ± 0.3	ND
	Liver	12.8 ± 1.6	10.9 ± 2.0	10.5 ± 1.2	9.6 ± 2.4	7.6 ± 1.7	4.7 ± 0.8	2.5 ± 0.6	1.5 ± 0.5	0.7 ± 0.5
	Kidney	258 ± 71.9	212 ± 40.8	191 ± 55.0	89.9 ± 42.4	30.6 ± 6.1	7.7 ± 4.3	1.9 ± 0.6	0.7 ± 0.4	0.2 ± 0.2
	Spleen	11.9 ± 1.2	12.5 ± 2.6	15.4 ± 1.9	10.6 ± 4.3	9.7 ± 4.8	6.4 ± 2.8	4.6 ± 1.8	3.4 ± 1.9	2.2 ± 1.6

[a] Antibiotic was intravenously administered at a dose of 20 mg/kg.
[b] Expressed as mean ± standard deviation (n = 8 to 10). ND, not detected.

TABLE 3. Concentrations of SCE-2787[a] in plasma and tissues of rabbits, dogs, and monkeys

Animal (n)	Plasma or tissue	Concn (μg/ml or μg/g)[b] after:		
		1/4 h	2 h	6 h
Rabbit (3)	Plasma	78.3 ± 6.3	10.5 ± 1.8	0.46[c]
	Lung	36.1 ± 12.1	7.8 ± 1.8	1.3 ± 0.4
	Liver	11.0 ± 0.9	10.7 ± 1.8	1.4 ± 1.0
	Kidney	220 ± 63.1	27.0 ± 3.1	5.9 ± 4.0
	Spleen	10.6 ± 1.0	2.4 ± 0.3	0.8 ± 0.5
Dog (3)	Plasma	55.6 ± 1.0	12.5 ± 1.4	0.65 ± 0.27
	Lung	18.1 ± 2.5	6.1 ± 0.8	1.0 ± 0.01
	Liver	30.2 ± 3.3	10.4 ± 2.6	6.3 ± 1.1
	Kidney	76.4 ± 12.5	37.0 ± 5.6	9.0 ± 4.3
	Spleen	7.0 ± 0.6	2.5 ± 0.2	0.7 ± 0.1
Monkey (4)	Plasma	95.9 ± 24.6	22.4 ± 5.2	1.2 ± 0.1
	Lung	45.6 ± 10.2	9.3 ± 3.0	0.6 ± 0.03
	Liver	32.4 ± 8.4	21.9 ± 13.6	5.7 ± 0.7
	Kidney	440 ± 295	125 ± 34.5	12.9 ± 1.4
	Spleen	16.1 ± 5.2	2.9 ± 0.7	0.7 ± 0.1

[a] SCE-2787 was intravenously administered at a dose of 20 mg/kg.
[b] Expressed as mean ± standard deviation (n = 3 to 4).
[c] n = 2.

In the present study, the pharmacokinetic properties of SCE-2787 were tested in mice, rats, rabbits, dogs, and monkeys. SCE-2787 was readily absorbed and distributed to the tissues, and the concentrations of SCE-2787 in the plasma, kidneys, and lungs attained after a 20-mg/kg dose was administered intravenously to the above-mentioned species were far greater than MICs for 90% of strains of SCE-2787 against the most clinically important bacteria, including *S. aureus* and *P. aeruginosa* (3). Biliary recovery of SCE-2787 was low; however, the concentrations of SCE-2787 were sufficient to inhibit most species of aerobic gram-positive and gram-negative bacteria. This suggests that SCE-2787 could be effectively used to treat infections caused by most gram-positive and gram-negative bacteria in the above-mentioned tissues and body fluids.

The pharmacokinetics of SCE-2787 in plasma in both mice and dogs were found to be very similar to those of ceftazidime, cefpirome, and cefclidin, but differences were seen in urinary excretion: the urinary recovery of SCE-2787 was slightly higher than that of ceftazidime and cefclidin. In monkeys given a 20-mg/kg intravenous dose of SCE-2787, the plasma AUC was larger and the $t_{1/2}$ was longer than the respective values in the other animals. The AUC and $t_{1/2}$ in monkeys were comparable to those in the healthy male

TABLE 4. Penetration of SCE-2787[a] in CSF of rats and rabbits

Animal (n)	Plasma or CSF	Parameter[b]				
		T_{max} (h)	C_{max} (μg/ml)	AUC (μg · h/ml)	$t_{1/2}$ (h)	Penetration ratio (%)[c]
Rat (8)	Plasma	—	—	35.5	0.25	—
	CSF	0.2	0.8	1.64	1.84	4.6
Rabbit (5)	Plasma	—	—	203	2.30	—
	CSF	1.7	1.3	13.0	5.63	6.4

[a] SCE-2787 was intravenously administered at a dose of 20 mg/kg.
[b] See the text for the parameter analysis. T_{max}, time to maximum drug concentration; C_{max}, maximum drug concentration; —, not determined.
[c] Penetration ratio: AUC in CSF/AUC in plasma.

TABLE 5. Urinary concentrations and excretion of SCE-2787[a] in animals

Animal (n)	Period (h)	Concn (μg/ml)[b]	Excretion (%)[b]
Mouse (15)	0–8	434 ± 82.6	83.9 ± 9.9
	8–24	1.8 ± 1.8	1.1 ± 1.3
	Total (0–24)		85.0 ± 9.7
Rat (8)	0–8	1,230 ± 410	72.3 ± 6.3
	8–24	8.4 ± 5.3	2.1 ± 1.4
	Total (0–24)		74.4 ± 6.4
Rabbit (5)	0–1	1,680 ± 662	32.0 ± 6.4
	1–2	1,080 ± 219	22.1 ± 9.6
	2–4	794 ± 230	19.2 ± 4.8
	4–6	393 ± 321	8.8 ± 5.6
	6–8	181 ± 142	3.2 ± 2.4
	8–24	46.0 ± 27.8	3.3 ± 1.9
	Total (0–24)		88.6 ± 4.1
Dog (5)	0–1	13,030 ± 6,340	45.5 ± 13.3
	1–2	8,370 ± 2,220	26.8 ± 10.5
	2–4	3,220 ± 862	13.3 ± 1.5
	4–6	860 ± 508	3.3 ± 1.0
	6–8	287 ± 170	0.8 ± 0.3
	Total (0–8)		89.7 ± 11.7
Monkey (4)	0–8	815 ± 114	81.1 ± 4.5
	8–24	19.5 ± 5.6	1.2 ± 0.1
	Total (0–24)		82.3 ± 4.4

[a] SCE-2787 was intravenously administered at a dose of 20 mg/kg.
[b] Expressed as mean ± standard deviation (n = 4 to 15).

TABLE 6. Biliary concentrations and excretion of SCE-2787[a] in animals

Animal (n)	Period (h)	Concn (μg/ml)[b]	Excretion (%)[b]
Mouse (7)	0–1	11.8 ± 5.3	0.35 ± 0.22
	1–2	11.7 ± 3.1	0.49 ± 0.18
	2–4	6.8 ± 2.5	0.14 ± 0.09
	4–6	4.8 ± 2.3	0.12 ± 0.06
	6–24	1.6 ± 1.7	0.20 ± 0.20
	Total (0–24)		1.30 ± 0.28
Rat (5)	0–1	18.3 ± 3.5	0.43 ± 0.15
	1–2	20.6 ± 8.6	0.40 ± 0.15
	2–4	8.6 ± 3.7	0.32 ± 0.12
	4–6	3.7 ± 3.3	0.12 ± 0.10
	6–8	1.8 ± 2.2	0.05 ± 0.06
	8–24	0.3 ± 0.2	0.04 ± 0.03
	Total (0–24)		1.36 ± 0.42
Rabbit (5)	0–1	8.2 ± 1.6	0.09 ± 0.02
	1–2	8.8 ± 2.9	0.08 ± 0.03
	2–4	5.0 ± 3.0	0.08 ± 0.04
	4–6	4.1 ± 2.9	0.05 ± 0.02
	6–8	3.8 ± 2.9	0.04 ± 0.02
	8–24	2.8 ± 1.5	0.12 ± 0.06
	Total (0–24)		0.46 ± 0.15
Dog (3)	0–1	16.7 ± 5.1	0.04 ± 0.01
	1–2	31.9 ± 18.9	0.06 ± 0.02
	2–4	19.8 ± 12.2	0.08 ± 0.02
	4–6	7.8 ± 3.3	0.03 ± 0.01
	6–8	5.1 ± 2.3	0.02 ± 0.01
	8–24	2.3 ± 2.8	0.05 ± 0.05
	Total (0–24)		0.28 ± 0.05

[a] SCE-2787 was intravenously administered at a dose of 20 mg/kg.
[b] Expressed as mean ± standard deviation (n = 3 to 7).

subjects given a 1,000-mg intravenous dose in a phase I clinical study (unpublished data).

The levels of SCE-2787 and ceftazidime in plasma in young dogs were lower than those in mature dogs. It has been shown that the volume of extracellular fluids per kilogram of body weight in young animals and humans is larger than that in mature animals and humans: the V of β-lactam antibiotics at steady state in the infants is generally greater than that in the adults (5, 9). This may be due to the fact that the CL_P and V in young dogs were larger than those in mature dogs (Table 1).

The protein-binding rate of SCE-2787 in the sera of animals and humans was very low and similar to those of cefclidin, ceftazidime (7), and cefpirome (8). SCE-2787 in the body fluids and tissues appears to be mainly in a free state, i.e., not bound to proteins. Merrikin et al. (4) have reported that β-lactam antibiotics with higher protein-binding capacities in mouse serum have longer $t_{1/2}$s in serum, but others (2, 10) could not demonstrate such a correlation. SCE-2787 has very similar protein binding in all animal species tested, yet it has fairly different $t_{1/2}$s in serum between rodents and other animals, such as monkeys, dogs, and rabbits, in which SCE-2787 is excreted through glomerular filtration and a part of renal tubular reabsorption (unpublished data). There may be a complex relationship among serum protein binding, elimination $t_{1/2}$, and the renal clearance mechanism.

SCE-2787 levels in the kidneys were high and greater than the levels in plasma and the other tissues in all five species tested. Thus, this distribution pattern in tissue was reflected in the urinary and biliary recovery rates: the urinary recov-

TABLE 7. Binding of SCE-2787 and cefclidin to serum protein from animals and humans

Serum source	Binding (%)[a] of:	
	SCE-2787	Cefclidin
Mouse	7.1	9.8
Rat	6.4	10.4
Rabbit	9.8	7.3
Dog	10.4	8.4
Monkey	10.9	8.1
Human	8.1	8.5
HSA[b]	8.2	6.6

[a] Determined by centrifugal ultrafiltration. Antibiotic concentration tested: 20 μg/ml.
[b] 4% human serum albumin.

ery of SCE-2787 (85.0, 74.4, 88.6, 89.7, and 82.3% in mice, rats, rabbits, dogs, and monkeys, respectively) was higher than the biliary recovery (1.30, 1.36, 0.46, and 0.28% in mice, rats, rabbits, and dogs, respectively).

In rats given 20 mg of SCE-2787 per kg once daily for 7 days, there was no accumulation in tissues or any delay in urinary excretion.

No active metabolites of SCE-2787 could be detected in the plasma or urine of mice, rats, rabbits, dogs, and monkeys by the thin-layer chromatography–bioautography.

In conclusion, upon intravenous administration SCE-2787 readily penetrates the tissues and is excreted mainly in the urine without being metabolized. Its pharmacokinetic profile is similar to those of ceftazidime, cefpirome, and cefclidin.

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