# METABOLIC FATE OF SCE-963, A NEW BROAD-SPECTRUM CEPHALOSPORIN, AFTER PARENTERAL ADMINISTRATION IN RATS AND DOGS

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Intramuscularly injected $^{14}$C-SCE-963 was absorbed by rats to give a maximum plasma level at 10~15 minutes after dosing and an apparent half-life of 25 minutes. In this species, the plasma half-life after intravenous injection was 27 minutes. Intramuscular injection of the labeled antibiotic to dogs gave a peak plasma level at 30 minutes, followed by decay with a half-life of 53 minutes. In both rats and dogs, the plasma levels of radioactivity were essentially the same as those of the unchanged antibiotic, which was moderately bound to plasma protein. $^{14}$C-SCE-963 was hardly taken up by the erythrocytes of these animals.

After intramuscular administration of $^{14}$C-SCE-963 to rats, the tissue level of radioactivity was maximum at 15 minutes with the highest concentration in the kidney, followed by liver, plasma, intestine and lung, and the lowest in brain. Whole-body autoradiography of pregnant rats showed that $^{14}$C-SCE-963 scarcely crossed the placenta.

In both rats and dogs, larger amounts of the dosed radioactivity was excreted in urine as the unchanged antibiotic, the remainder appearing in feces *via* bile. This finding indicated that the metabolism of SCE-963 was only a minor process in the elimination of the antibiotic. $^{14}$C-SCE-963 was almost completely eliminated from the body of both animals within 24~48 hours. Radioactivity was detected in the milk of rats given $^{14}$C-SCE-963 intramuscularly.

SCE-963, 7$\beta$-[2-(2-aminothiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]-thio]methyl]-ceph-3-em-4-carboxylic acid, is a new injectable cephalosporin having a wide spectrum of activity for Gram-positive and Gram-negative organisms including indole-positive *Proteus* and clinical isolates of cefazolin-resistant *Escherichia coli* and *Klebsiella pneumoniae*.[1,2] The antibiotic is shown to be resistant to the hydrolysis by $\beta$-lactamases from various bacterial strains.[2] Recent clinical studies have established the effectiveness of SCE-963 in the treatment of infections of the respiratory system, genitourinary and biliary tracts and of peritonitis without notable side effects (Dr. K. SHIMIZU *et al.*, personal communication, Tokyo Women's Medical College, Tokyo, Japan).

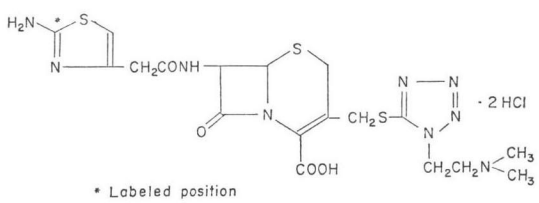
The aim of the present study was to determine the absorption, distribution and excretion of $^{14}$C-labeled SCE-963 in rats and dogs, in an attempt to provide a pharmacokinetic basis for the pharmacological effects.

## Materials and Methods

### 1. Materials

7$\beta$-[2-(2-Amino[2-$^{14}$C]thiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]-thio]methyl]-ceph-3-em-4-carboxylic acid dihydrochloride (Fig. 1) was synthesized in the Radioisotope Laboratory of this Division. Three samples with specific radioactivity of 22.5, 23.0 and 28.8 $\mu$Ci/mg were used. Radiopurity (>90

Fig. 1. 7$\beta$-[2-(2-Aminothiazol-4-yl)acetamido]-3-[[[1-(2-dimethylaminoethyl)-1H-tetrazol-5-yl]thio]methyl]-ceph-3-em-4-carboxylic acid dihydrochloride (SCE-963·2HCl).



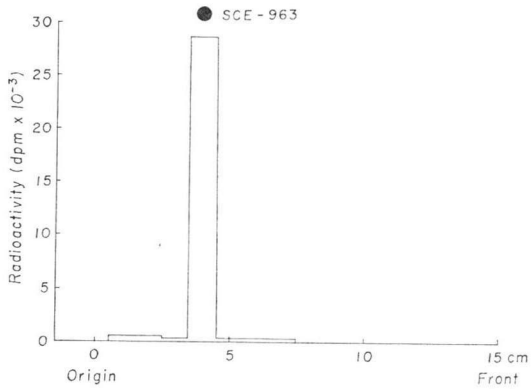
%) and chemical identity were verified by TLC (refer to Fig. 2). Non-labeled SCE-963·2HCl was synthesized in the Medicinal Research Laboratories of this Division.

2. Animals and Drug Administration

Animals used were male or female Sprague-Dawley rats (JCL-SD, CLEA Japan Inc., Tokyo, Japan) weighing 215~510 g and male beagles (CLEA Japan Inc., Tokyo, Japan) weighing 9.0~12.0 kg. They were maintained on laboratory chow (CE-2 for rats and CD-5 for dogs, CLEA Japan Inc., Tokyo, Japan) and drinking water in temperature-humidity-controlled rooms (26°C, 60%) with 12 hours' light-dark cycles for more than a week before use. $^{14}$C-SCE-963·2HCl diluted more than 7 times with the carrier was mixed with an equimolar amount of $Na_2CO_3$, dissolved in "parenteral" water and injected to animals as SCE-963. Intramuscular (i.m.) or intravenous (i.v.) dose of the labeled antibiotic was 20 mg (4.8~70.0 $\mu$Ci)/kg. Injection volumes were 1 ml/kg for rats and 0.2 ml/kg for dogs.

Fig. 2. A representative radio thin-layer chromatogram of dog urine after intramuscular administration of $^{14}$C-SCE-963.

The sample was the 6-hour urine from one dog (body wt. 9.9 kg) given i.m. $^{14}$C-SCE-963 at a dose of 20 mg (4.8 $\mu$Ci)/kg. Non-labeled SCE-963 (●) was used as an internal standard.




3. Collection of Biological Samples

Blood was taken from the tail vein or abdominal aorta in rats and from the cephalic vein in dogs. The spontaneous urine and feces were collected by using the usual metabolism cages equipped with urino-fecal separators. Radioactive carbon dioxide in the expired air of rats was absorbed in 5 M KOH.[3] Bile samples were obtained after cannulation of the common bile duct of rats and dogs anesthetized with pentobarbital sodium (i.m. 50 mg/kg for rats and i.v. 30 mg/kg for dogs). In dogs, the cystic duct was ligated before cannulation of the common bile duct. Urine and bile samples were collected under freezing with solid carbon dioxide and kept as such until analyzed.

4. Analytical Methods

Measurement of Radioactivity: Radioactivity was measured with a liquid scintillation counter (model LSC-683, Aloka Co. Ltd., Tokyo, Japan) with an automatic quenching monitor and on-line digital computer (model JAC-2, Japan Radio Co. Ltd., Tokyo, Japan) for data processing. Radioactivity in plasma, urine, bile and milk was counted directly in a toluene-phosphor mixture containing non-ionic detergent.[4] Blood radioactivity was determined in the same way after decolorizing with $H_2O_2$ as described previously.[5] Radioactivity in tissues and feces was determined by using a sample oxidizer (model 306, Packard Instrument Co. Inc., Downers Grove, U.S.A.). Respiratory $^{14}CO_2$ trapped in 5 M KOH was counted in a toluene-phosphor mixture[3] after regeneration and reabsorption into Hyamine 10-X solution (Packard Instrument Co. Inc., Downers Grove, U.S.A.).

Measurement of antibacterial activity: Antibacterial concentrations in biological fluids were determined by the agar-well diffusion technique using *Proteus mirabilis* ATCC 21100 as the test organism. The samples were diluted with 0.1 M potassium phosphate buffer (pH 7.0) to the final concentration of the antibiotic of less than 40 $\mu$g/ml. The calibration curve in each experiment was prepared using the respective $^{14}$C-SCE-963 solution dosed after appropriately diluting with the phosphate buffer.

TLC analysis: $^{14}$C-SCE-963 in urine and bile was quantitatively determined by TLC using precoated silica gel $60F_{254}$ plates (0.25 mm thickness, E. Merck, Darmstadt, Germany). The solvent system used was acetonitrile - acetic acid - 0.5 M sodium chloride (15 : 1 : 6, v/v). $^{14}$C-SCE-963 on the dried thin-layer chromatograms was located by UV absorption of the non-labeled antibiotic added to the test samples as an internal standard or by bioautographic technique using *Proteus mirabilis* ATCC 21100 as the test organism. Fig. 2 depicts a typical radio thin-layer chromatogram of the 6-hour urine of the

dog given i.m. $^{14}$C-SCE-963.

5. Uptake by Erythrocytes

$^{14}$C-SCE-963 was added to the blood of rats and dogs *in vitro* at a concentration of 5~100 $\mu$g/ml. After incubating for 1 hour at 25°C, radioactivity in the whole blood and plasma was determined on the same blood samples. The percentage of the antibiotic taken up by the erythrocytes was calculated using the hematocrit value.[5]

6. Plasma Protein Binding

Binding of $^{14}$C-SCE-963 to the plasma protein of rats and dogs was determined by the ultracentrifugation method. The plasma samples to which the labeled antibiotic was added *in vitro* at a concentration of 10~50 $\mu$g/ml were centrifuged for 6 hours at 300,000 × $g$ using an ultracentrifuge (Hitachi model 65P with a model RPS-65T swing roter, Hitachi Ltd., Tokyo, Japan).

7. Whole-body Autoradiography

Whole-body sections (40 $\mu$ thickness) of male rats were prepared at 5 minutes, 15 minutes, 1, 6 and 24 hours after i.m. dose of $^{14}$C-SCE-963 by the method of ULLBERG[6] and exposed to X-ray film (Industrial type, Fuji Photo Film Co. Ltd., Tokyo, Japan) for 15 days at 4°C. Placental transfer of $^{14}$C-SCE-963 was also studied by whole-body autoradiography in pregnant rats on the 18th to 19th day of gestation.

8. Lacteal Excretion

Milk was collected at 1, 4 and 6 hours after intramuscular injection of $^{14}$C-SCE-963 to rats on the 20th day after parturition, as described elsewhere.[7]

## Results

### 1. Plasma Levels

Plasma levels of radioactivity were studied after intramuscular or intravenous injection of $^{14}$C-SCE-963 in rats and dogs (Fig. 3). In rats given the labeled antibiotic intramuscularly, the plasma level of radioactivity was maximum at 10~15 minutes (18 $\mu$g eq. of SCE-963/ml) after dosing and then declined with a half-life of 25 minutes. After intravenous injection to rats, the plasma radioactivity fell off biphasically with respective half-lives of 4.5 minutes (0~5 minutes, distribution phase) and 27 minutes (5~120 minutes, elimination phase). The plasma level after intramuscular administration to dogs peaked at 30 minutes (40 $\mu$g eq. of SCE-963/ml), followed by decay with a half-life of 53 minutes.

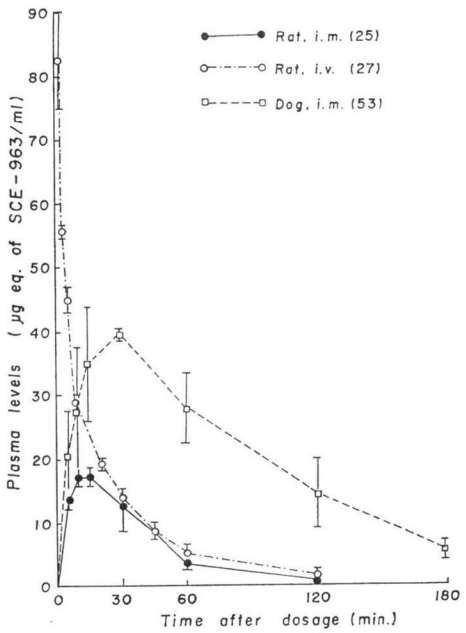
### 2. Distribution

Distribution into Erythrocytes:

More than 91% of $^{14}$C-SCE-963 added to the blood of rats and dogs *in vitro* at a concentration of 5~100 $\mu$g/ml was present in the plasma fraction. This finding indicated that the antibiotic was hardly taken up by the erythrocytes of

Fig. 3. Plasma levels of radioactivity after intramuscular or intravenous administration of $^{14}$C-SCE-963 in rats and dogs.

Rats (av. body wt. 219 g) and dogs (av. body wt. 10.1 kg) were given i.m. or i.v. $^{14}$C-SCE-963 at a dose of 20 mg (14.5~35.4 $\mu$Ci)/kg. Plasma levels are expressed as the mean±S.D. of three animals in each experiment. Apparent half-lives shown in parentheses were calculated using linear regression analysis.



these animals.

Tissue Levels:

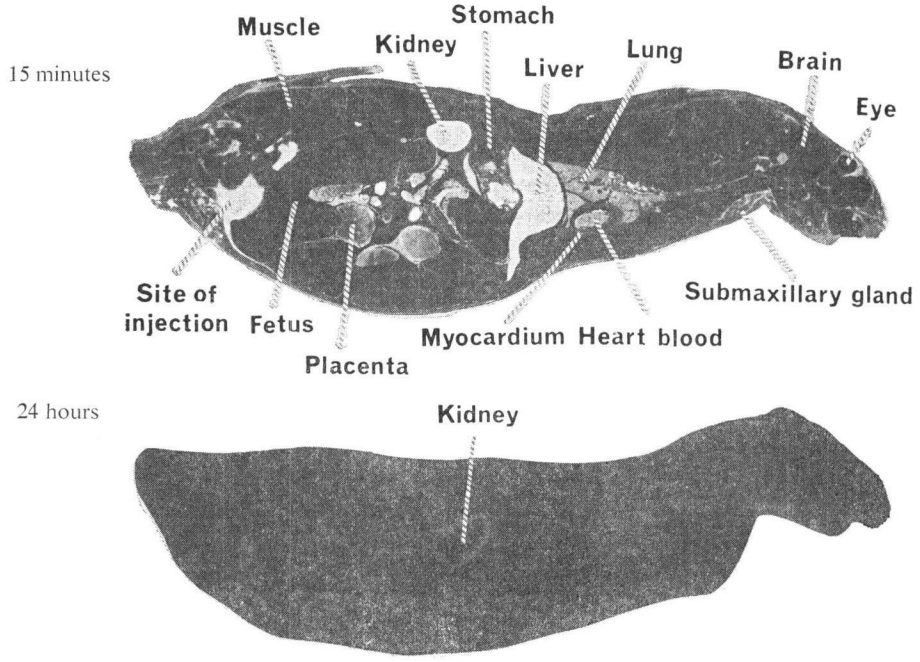
Tissue distribution of i.m. $^{14}$C-SCE-963 was preliminarily studied in rats by whole-body auto-

Table 1. Tissue levels of radioactivity after intramuscular administration of $^{14}$C-SCE-963 in rats

| Tissue | Tissue level ($\mu$geq. of SCE-963/g or ml) | | |
|---|---|---|---|
| | 15 minutes | 2 hours | 24 hours |
| Plasma | 26.0± 2.6 | 1.9± 0.2 | 0.7± 0.1 |
| Brain | 0.5± 0.0 | 0.1± 0.0 | 0.0± 0.0 |
| Spinal cord | 0.7± 0.0 | 0.2± 0.2 | 0.1± 0.0 |
| Thymus | 3.0± 0.4 | 0.4± 0.1 | 0.2± 0.1 |
| Heart | 3.9± 0.8 | 0.4± 0.1 | 0.2± 0.1 |
| Lung | 8.3± 2.0 | 1.1± 0.3 | 0.4± 0.0 |
| Liver | 27.3± 7.0 | 1.1± 0.2 | 0.3± 0.0 |
| Kidney | 120.3±17.0 | 11.2± 1.3 | 4.8± 1.6 |
| Spleen | 3.1± 0.5 | 0.4± 0.0 | 0.2± 0.0 |
| Stomach | 5.3± 1.9 | 0.4± 0.2 | 0.2± 0.1 |
| Intestine | 16.7±12.7 | 15.6±12.6 | 0.6± 0.0 |
| Adrenal | 4.8± 3.4 | 0.7± 0.3 | 1.0± 0.2 |
| Pancreas | 1.6± 0.4 | 0.4± 0.0 | 0.2± 0.0 |
| Testis | 2.6± 0.7 | 0.3± 0.1 | 0.2± 0.0 |
| Adipose | 2.6± 0.1 | 0.6± 0.3 | 0.4± 0.1 |
| Muscle | 2.3± 0.6 | 0.2± 0.0 | 0.1± 0.0 |

Rats (av. body wt. 263 g) were given i.m. $^{14}$C-SCE-963 at a dose of 20 mg (29.1 $\mu$Ci)/kg. Data are the mean ±S.D. of three rats.

Fig. 4. Whole-body autoradiography in pregnant rats after intramuscular administration of $^{14}$C-SCE-963.
Female rats (av. body wt. 480 g) on the 18th to 19th day of gestation were given i.m. $^{14}$C-SCE-963 at a dose of 20 mg (70.0 $\mu$Ci)/kg. Autoradiograms were taken at 15 minutes and 24 hours after dosing.



radiography. The results showed that radioactive concentrations in tissues generally attained a peak at 15 minutes with the highest concentration in the kidney and thereafter declined rapidly to low levels at 24 hours. Based on these findings, tissue levels of radioactivity were then determined at 15 minutes, 2 and 24 hours after intramuscular administration of $^{14}$C-SCE-963 in rats (Table 1). At 15 minutes after dosing, the radioactivity was the highest in the kidney, followed by liver, plasma, intestine and lung, and the lowest in brain. The radioactivities in most tissues fell off to very low levels within 24 hours except for the kidney, in which a relatively higher concentration of radioactivity still remained.

Placental Transfer:

Placental transfer of the antibiotic was examined in pregnant rats using a whole-body autoradiographic technique (Fig. 4). At any time after intramuscular dosing of $^{14}$C-SCE-963, no detectable amount of radioactivity was present in the fetus, showing that the antibiotic hardly crossed the placenta. The distribution pattern of radioactivity in maternal tissues was similar to that in male rats (Table 1).

### 3. Plasma Protein Binding

*In vitro* studies using $^{14}$C-SCE-963 (5~50 μg/ml) showed that the antibiotic was 47~51% bound in rats and 24% in dogs (Table 2).

Table 2. Plasma protein binding of $^{14}$C-SCE-963 in the rat and dog

| Plasma concn. of $^{14}$C-SCE-963 (μg/ml) | % Binding | |
|---|---|---|
| | Rat | Dog |
| 5 | 47.0 | 23.6 |
| 10 | 50.9 | 23.0 |
| 50 | 47.0 | 23.5 |

The binding was estimated by the ultracentrifugation method using 5 ml of the plasma containing the labeled antibiotic.

### 4. Excretion

Urinary and Fecal Excretions:

After intramuscular or intravenous administration of $^{14}$C-SCE-963 to rats and dogs, elimination of radioactivity was almost complete within 24~48 hours with more radioactivity appearing in urine than in feces (Table 3). In both animals, approximately half of the injected radioactivity was excreted in the urine during the first 6~8 hours after dosing. No detectable amount of radioactivity was excreted in the expired air of rats.

Biliary Excretion and Reabsorption:

Biliary excretion of the radioactive antibiotic was studied in rats and dogs with biliary-cannulas (Table 3). In rats, the biliary excretion was complete in 2 hours after dosage, 17% and 23% of the injected radioactivity being excreted after intramuscular and intravenous administration, respectively. Fecal elimination of radioactivity in the biliary-cannulated rats given i.v. $^{14}$C-SCE-963 was much less (1.5% of the dose in 24 hours) than that in the intact rats, indicating that the fecal radioactivity in the latter animals was due to the hepato-biliary excretion. After intramuscular injection to dogs, 12% of the dose was recovered from the 6-hour bile.

An entero-hepatic cycling of the biliary radioactivity was examined by the following experiments. The radioactive bile, obtained from three rats given i.m. $^{14}$C-SCE-963, was injected into three other rats (0.58 mg eq. of SCE-963) intraduodenally. In 24 hours, 3.9% and 21% of the dosed radioactivity were excreted in bile and urine, respectively. This finding indicates that only about 4% of the i.m. 20 mg/kg dose of the antibiotic was reabsorbed from the intestine, since the biliary excretion is 17% of the dose after the intramuscular injection (Table 3).

Lacteal Excretion:

Radioactivity was detectable in rat milk after intramuscular administration of $^{14}$C-SCE-963

Table 3. Cumulative excretion of radioactivity in urine, feces and bile after intramuscular or intravenous administration of $^{14}$C-SCE-963 in rats and dogs

| Species | Route of administration | Time after dosage (hours) | Excretion into (% of dose) | | | Total radioactivity recovered (% of dose) |
|---|---|---|---|---|---|---|
| | | | Urine | Feces | Bile | |
| Rat | i.m. (n=5) | 6 | 59.8± 6.5 | n.d. | n.d. | n.d. |
| | | 24 | 68.2± 0.1 | 28.4± 4.8 | n.d. | 96.7± 3.5 |
| | | 48 | 69.7± 1.4 | 30.5± 1.2 | n.d. | 100.3± 2.7 |
| | i.v. (n=3) | 6 | 47.6± 6.1 | n.d. | n.d. | n.d. |
| | | 24 | 55.1± 4.5 | 34.5± 1.8 | n.d. | 89.6± 3.6 |
| | | 48 | 57.6± 3.2 | 42.2± 1.7 | n.d. | 99.8± 2.4 |
| | i.m. (n=3) | 2 | n.d. | n.d. | 16.7± 7.6 | n.d. |
| | | 4 | n.d. | n.d. | 17.4± 7.4 | n.d. |
| | | 6 | 73.9±10.1 | n.d. | 17.5± 7.4 | 91.5±10.2 |
| | i.v. (n=3) | 2 | n.d. | n.d. | 23.2± 3.4 | n.d. |
| | | 4 | n.d. | n.d. | 23.6± 3.4 | n.d. |
| | | 6 | 58.6± 1.4 | n.d. | 23.6± 3.3 | 82.2± 4.7 |
| Dog | i.m. (n=3) | 8 | 55.0±12.3 | n.d. | n.d. | n.d. |
| | | 24 | 61.7± 5.7 | 23.1± 4.9 | n.d. | 85.0± 8.2 |
| | | 48 | 64.9± 4.7 | 28.6± 7.3 | n.d. | 91.2± 4.6 |
| | i.m. (n=2)* | 2 | 38.7 (41.3, 36.0) | n.d. | 5.5 ( 5.8, 5.1) | 44.1 (47.1, 41.1) |
| | | 4 | 61.5 (59.7, 63.2) | n.d. | 10.1 (11.0, 9.1) | 71.5 (70.7, 72.3) |
| | | 6 | 74.1 (71.5, 76.7) | n.d. | 11.7 (12.7, 10.6) | 85.8 (84.2, 87.3) |

Rats (av. body wt. 246 g) and dogs (av. body wt. 9.9 kg) were given i.m. or i.v. $^{14}$C-SCE-963 at a dose of 20 mg (4.8~65.5 $\mu$Ci)/kg. Data are the mean ±S.D., unless otherwise noted.

* Mean values with data on the individual animals in parentheses.

n.d.: not determined.

Table 4. Lacteal excretion of radioactivity after intramuscular injection of $^{14}$C-SCE-963 in rats

| Time after dosage (hours) | Concn. of radioactivity ($\mu$g eq. of SCE-963/ml) | |
|---|---|---|
| | Plasma | Milk |
| 1* | 10.0 (12.0, 7.9) | 1.3 (0.9, 1.7) |
| 4 | 2.2±0.9 | 1.0±0.4 |
| 6 | 1.1±0.1 | 1.2±1.0 |

Female rats (av. body wt. 380 g) on the 20th day after parturition were given i.m. $^{14}$C-SCE-963 at a dose of 20 mg (65.2 $\mu$Ci)/kg. Data are the mean ±S.D. of three rats, unless otherwise noted.

* Mean values with data on the individual animals in parentheses.

(Table 4).

### 5. Composition of Radioactivity in Biological Fluids

Unchanged SCE-963 in plasma, urine and bile was quantitatively determined by TLC or bioassay (Figs. 5 and 6). In both rats and dogs, plasma levels of radioactivity were essentially the same as those of the unchanged antibiotic estimated by bioassay (Fig. 5). As evidenced by TLC, urinary and biliary radioactivities were derived mostly from unchanged SCE-963 in both rats and dogs (Fig. 6). It was confirmed by bioautography that SCE-963 was the only component with antibacterial activity in urine and bile of these animals. In addition, urinary and biliary contents of SCE-963 estimated by bioassay were fairly consistent with those quantified by TLC (Fig. 6).

Fig. 5. Radioactive and antibacterial concentrations in the plasma of rats and dogs given $^{14}$C-SCE-963 intramuscularly.

Rats (av. body wt. 247 g) and dogs (av. body wt. 10.1 kg) were given i.m. $^{14}$C-SCE-963 at a dose of 20 mg (14.5~29.1 $\mu$Ci)/kg. Data are the mean ±S.D. of three to six rats and three dogs.

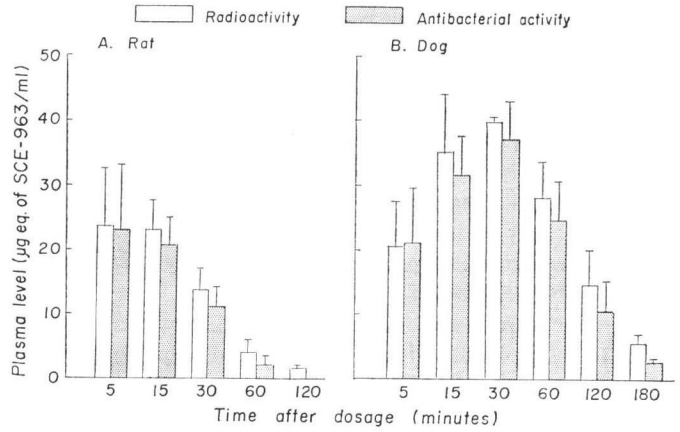
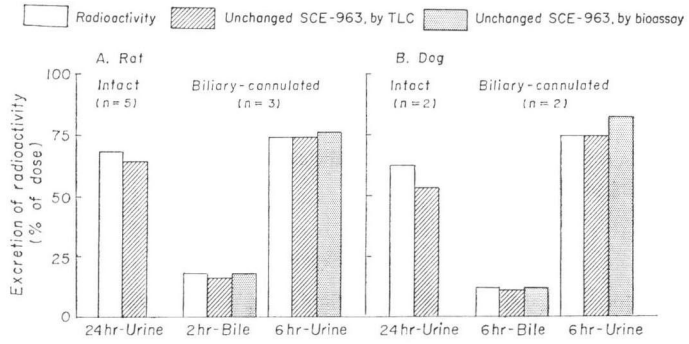



Fig. 6. Urinary and biliary excretions of unchanged SCE-963 after intramuscular injection of the labeled antibiotic in rats and dogs.

The rats and dogs corresponding to Table 3 were used. Excretion of radioactivity is expressed as the mean value for the number of animals in parentheses. Excretions of unchanged SCE-963, estimated by TLC or bioassay, are values for pooled samples.




## Discussion

The present studies have clarified the metabolic fate of SCE-963 in rats and dogs. A rapid and quantitative absorption of intramuscularly injected SCE-963 in both animals was evidenced by the following findings: (1) immediate appearance of the antibiotic in the circulation and (2) the urinary and fecal recoveries that amounted to almost 100% of the administered dose. It must be mentioned, however, that the rate of absorption of SCE-963, like other cephalosporins,[8] seems to be somewhat slower in dogs than in rats, as suggested by the longer time to the peak plasma level and the slower disappearance from the plasma in the former animals.

A species difference has been recognized in the plasma protein binding of cephalosporins.[8,9] SCE-963 is bound 47~51% in rats and 24% in dogs, the binding being rather less extensive than that of other cephalosporins.[8] The plasma protein binding of a drug could affect its biological activities or metabolism. As described above, SCE-963 exhibits moderate protein binding and a study of TSUCHIYA *et al.*[2] showed that the addition of horse serum to the antibiotic caused no significant change in the antibacterial activity. The present study demonstrated a rapid tissue distribution and elimination of

SCE-963. It thus appears that the plasma protein binding does not profoundly affect the metabolic disposition of SCE-963.

SCE-963 is widely distributed in rat tissues with much higher concentration in the kidney. During the first 2 hours after dosing, the renal concentration of SCE-963 is higher than the MICs against most strains of Gram-positive and Gram-negative bacteria.[2] Significant levels of the antibiotic were also demonstrated in other tissues, including the liver, intestine and lung. SCE-963 was scarcely transferred into the rat fetus, the result being similar to that obtained with cephacetrile,[4] cefatrizine[10] and cefazolin.[11] It was also shown that the concentration of SCE-963 in the rat milk was very low.

As has been reported on cephacetrile,[4] cephaloglycin,[12] cephalothin[13,14] and cephapirin,[15] some cephalosporins are metabolized by desacetylation at the C-3 methyl position and/or by hydrolysis of the amide linkage. This metabolic degradation does, however, not occur with SCE-963, since a study in rats and dogs using TLC and bioassay showed that no significant amount of metabolites was present in the plasma, urine and bile. Thus, it appears that metabolic degradation of SCE-963 is only a minor process in the elimination of the antibiotic.

Extensive renal excretion, carried out by the processes of glomerular filtration and tubular secretion, is a property shared by most cephalosporins.[16] In rats and dogs, a greater part of the administered dose of SCE-963 is eliminated from the body also through renal excretion, with the more appreciable amount appearing in the feces *via* hepato-biliary route. Preliminary studies (unpublished data by the present authors) indicated that 91.7% of the intramuscular dose of SCE-963 was excreted in the 6-hour bile of rats when the renal pedicles were tied to prevent urinary excretion. The above excretory pattern of SCE-963 seems, therefore, to indicate more rapid renal excretion of the antibiotic. In this respect, the finding is of interest that the fecal excretion *via* bile of intravenous SCE-963 predominates over that of the intramuscular antibiotic. This phenomenon might be explicable by the increased hepatic SCE-963 available for biliary excretion after intravenous administration.

In conclusion, intramuscular SCE-963 is rapidly absorbed, widely distributed in tissues and excreted unchanged largely in urine with the remainder appearing in bile.

Acknowledgements

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## References

1) NUMATA, M.; I. MINAMIDA, M. YAMAOKA, M. SHIRAISHI, T. MIYAWAKI & T. NISHIMURA: SCE-963, a new cephalosporin. I. Synthesis and structure. 17th Intersci. Conf. Antimicr. Agents & Chemoth., New York, U.S.A., October 12~14, 1977
2) TSUCHIYA, K.; M. KIDA, M. KONDO, S. GOTO & S. KUWAHARA: SCE-963, a new cephalosporin. II. *In vitro* and *in vivo* antibacterial activities. 17th Intersci. Conf. Antimicr. Agents & Chemoth., New York, U.S.A., October 12~14, 1977
3) TANAYAMA, S.; T. FUJITA, Y. SHIRAKAWA & Z. SUZUOKI: Metabolic fate of 5-ethoxycarbonyl-3-morpholinosydnonimine (SIN-10). 1. Absorption, excretion and tissue distribution in rats and mice. Jap. J. Pharmacol. 20: 413~423, 1970
4) NAKAI, Y.; Y. KANAI, T. FUGONO & S. TANAYAMA: Metabolic fate of cephacetrile after parenteral administration in rats and rabbits. J. Antibiotics 29: 81~90, 1976
5) TANAYAMA, S.; Y. SHIRAKAWA, Y. KANAI & Z. SUZUOKI: Metabolism of 8-chloro-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (D-40TA), a new central depressant. I. Absorption, distribution and excretion in rats. Xenobiotica 4: 33~47, 1974
6) ULLBERG, S.: Studies on the distribution and fate of $^{35}$S-labelled benzylpenicillin in the body. Acta Radiol., Suppl. 118: 1~110, 1954
7) TANAYAMA, S.; S. MOMOSE, Y. KANAI & Y. SHIRAKAWA: Metabolism of 8-chloro-6-phenyl-4*H*-*s*-triazolo-[4,3-*a*][1,4]benzodiazepine (D-40TA), a new central depressant. IV. Placental transfer and excretion in milk in rats. Xenobiotica 4: 219~227, 1974
8) NISHIDA, M.; T. MURAKAWA, T. KAMIMURA, N. OKADA, H. SAKAMOTO, S. FUKADA, S. NAKAMOTO, Y.

YOKOTA & K. MIKI: *In vitro* and *in vivo* evaluation of ceftezole, a new cephalosporin derivative. Antimicr. Agents & Chemoth. 10: 1~13, 1976

9) NISHIDA, M.; T. MURAKAWA, T. KAMIMURA, N. OKADA, H. SAKAMOTO, S. FUKADA, S. NAKAMOTO, Y. YOKOTA & K. MIKI: Laboratory evaluation of FR10612, a new oral cephalosporin derivative. J. Antibiotics 29: 444~459, 1976
10) MATSUZAKI, M.; H. MATSUMOTO, K. OCHIAI, Y. TASHIRO, M. HINO, K. SUZUKI & M. SEKINO: Absorption, distribution and excretion of $^{14}$C-cefatrizine ($^{14}$C-S-640P) in rats. Jap. J. Antibiotics 29: 391~402, 1976
11) KOZATANI, J.; M. OKUI, K. NODA, T. OGINO & H. NOGUCHI: Cefazolin, a new semisynthetic cephalosporin antibiotic. V. Distribution of cefazolin-$^{14}$C in mice and rats after parenteral administration. Chem. Pharm. Bull. (Tokyo) 20: 1105~1113, 1972
12) SHIMIZU, K. & H. NISHIMURA: Problems in the bio-assay of orally administered cephaloglycin in biological fluids and method for the detection of its metabolites, desacetylcephaloglycin. J. Antibiotics 23: 216~222, 1970
13) LEE, C. C.; E. B. HERR & R. C. ANDERSON: Pharmacological and toxicological studies on cephalothin. Clin. Med. 70: 1123~1138, 1963
14) HOEHN, M. M.; H. W. MURPHY, C. T. PUGH & N. E. DAVIS: Paper chromatographic techniques for the determination of cephalothin and desacetylcephalothin in body fluids. Appl. Microbiol. 20: 734~736, 1970
15) MCCLOSKEY, R. V.; E. E. TERRY, A. W. MCCRACKEN, M. J. SWEENEY & M. F. FORLAND: Effect of hemodialysis and renal failure on serum and urine concentrations of cephapirin sodium. Antimicr. Agents & Chemoth. 1: 90~93, 1972
16) NIGHTINGALE, C. H.; D. S. GREENE & R. QUINTILIANI: Pharmacokinetics and clinical use of cephalosporin antibiotics. J. Pharm. Sci. 64: 1899~1927, 1975