Absorption, Distribution and Excretion of SM-10888 in Rats

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Summary

9-Amino-8-fluoro-1, 2, 3, 4-tetrahydro-2, 4-methanoacridine citrate (SM-10888) was given to rats orally or intravenously, and its absorption, distribution and excretion were investigated.

1. After a single oral administration of ^{14}C -SM-10888 (5mg/kg), the serum ^{14}C level reached a maximum at 30min (1.09 μg eq./g), with an AUC value corresponding to about 90% of that observed after intravenous administration, clearly revealing rapid and efficient absorption from the gastrointestinal tract.

Under fasted conditions, C_{max} was 2-fold higher than that of non-fasted animals, without significant change in AUC, suggesting that diet causes delayed absorption. Both C_{max} and AUC increased as the dose was raised from 1 to 20mg/kg. Repeated dosing (5mg/kg/day for 14 days) exerted little effect on serum ^{14}C levels.

2. After a single oral administration of ^{14}C -SM-10888 (5mg/kg), the radioactivity was distributed throughout the body, with relatively higher activities being observed in the digestive tract, the liver and the salivary gland. Radioactivity in each tissue had drastically decreased by 24hr post administration.

3. After a single oral administration of ^{14}C -SM-10888 (5mg/kg), cumulative excretion into the urine and feces after 168hr was 52.2% and 44.2%, respectively. When administered to bile-duct cannulated rats, cumulative excretion after 72hr into the bile and urine was 65.1% and 29.1%, respectively, providing further support for a high absorption rate.

Repeated dosing had little effect on the patterns of excretion into the urine and feces.

Introduction

9-Amino-8-fluoro-1,2,3,4-tetrahydro-2,4-methanoacridine citrate (SM-10888) is a potent cholinesterase inhibitor, which is being developed as a promising drug for treatment of senile dementia of the Alzheimer type (SDAT). It has been reported that SDAT is related to a specific deficit of central cholinergic function^{1,2)} and when tacrine, a cholinesterase inhibitor, was applied to patients with SDAT, significant improvements were recorded^{3,4)}. SM-10888, a derivative of tacrine, was reported to have more desirable characteristics from animal studies in which it induced central cholinergic effects⁵⁾ and improved cognitive functions⁶⁾ at doses not causing any peripheral side effects.

In the present paper, the disposition of SM-10888 in rats is described.

Materials and methods

Materials

SM-10888 (Lot No. H-71) was synthesized by Sumitomo Pharmaceuticals Co., Ltd. Radiolabeled compound (¹⁴C-SM-10888, Lot No. C-88-054) (Fig. 1) was synthesized by Sumitomo Chemical Co., Ltd. Radiochemical purity determined by thin layer chromatography (TLC) and high performance liquid chromatography (HPLC) was over 99%. Chemical purity by HPLC was over 99%. Specific activity was 0.80 GBq/mmol (2.14 MBq/mg).

Fig. 1 Chemical structure of ¹⁴C-SM-10888
(* : labeled position)

Animals

Seven-week old male Sprague-Dawley rats (Charles River Japan) weighing 254-319 g were used.

After purchase as six week olds, animals were given diet (CE-2, Clea Japan) and water *ad libitum*, and housed in a temperature ($23 \pm 2^\circ\text{C}$), and humidity ($55 \pm 10\%$)-controlled environment with a 12hr light-dark (light : 8 : 00-20 : 00) cycle. Animals were housed for one week, and those without any abnormalities were submitted for experiments.

Administration of Drugs

¹⁴C-SM-10888 was mixed with unlabeled SM-10888 and given to rats as a distilled water solution for oral dosing, and as a saline solution for intravenous dosing. Drug was administered to the animals under non-fasted conditions, except where otherwise stated.

1. Oral administration

Drug solution was given to rats orally at dose of 5mg/10ml/kg using gavage needles.

To evaluate the effects of food on absorption, one group of rats were fasted for 24hr before dosing and refed starting 24hr after the administration. For the dose response study, 1 and 20mg/10ml/kg of dose were additionally given. The influence of repeated oral dosing was investigated using daily dose of 5mg/10ml/kg for 14 days.

2. Intravenous administration

Saline solution was injected into the femoral veins of rats at dose of 5mg/ml/kg using disposable needles.

Sampling

1. Serum

After the drug administration, rats were housed in standard cages (Immortal®, Okazaki Sangyo, Japan) and at the scheduled times, were anesthetized with ether (Kanto Chemical, Japan) to allow blood samples (ca. 0.3ml at each point) to be collected via the retroorbital plexus. These were subsequently centrifuged (3,000rpm, 10min, 4 °C) to obtain serum samples.

Blood collections were conducted at the following time point :

single dose : 5min (only i.v. study), 15, 30min, 1, 2, 4, 6, 24, 48 and 72hr.

repeated dose : 15, 30min, 1, 2, 4, 6 and 24hr (days 1 and 14), 30min and 24hr (days 2-13)

2. Tissue

After the drug administration, rats were housed in standard cages (Immortal®, Okazaki Sangyo, Japan) and after 30min, 2hr, 24hr and 72hr*, groups of animals were killed by exsanguination from the *vena cava* under ether anesthesia. The following tissues were then excised and washed with saline : cerebrum, cerebellum, pituitary*, salivary gland, thymus, heart, lung, liver, stomach, large intestine, small intestine, pancreas, spleen, adrenal, kidney, bladder, prostate*, testis, bone marrow, fat, muscle and skin.

(* : repeated dosing study only)

3. Urine and Feces

After the drug administration, rats were housed individually in metabolic cages (Metabolica®, Sugiyamagen Iriki, Japan), and at the scheduled times, accumulated urine and feces were collected separately. Urine samples were applied directly to radioactivity measurement. Feces samples were mixed with 5 % carboxymethyl cellulose (Kanto Chemical, Japan) solution, and then applied to radioactivity measurement.

Collection time points were as follows :

Single dose : 6, 24, 48, 72, 120 and 168hr.

Repeated dose : 6 and 24hr (day 1), 24hr (days 2-13), 6, 24, 48 and 72hr (day 14).

4. Bile

The bile-ducts were first cannulated with polyethylens tubes (PE-10, Clay Adams, USA). After single oral administration, rats were kept in Bollman cages (KN-326, Nat-

sume, Japan) and electrolytes (Solita-T3, Shimizu Pharmaceuticals, Japan) were given. Accumulated bile, urine and feces were collected separately at 6, 24, 48 and 72hr.

Determination of Radioactivity

0.1ml aliquots of serum were mixed with NCS[®] (Amersham, USA), then 15ml of TO LUENE SCINTILLATOR[®] (Pancard, USA) was added. Aliquots of tissue and feces samples (ca. 0.2 g) were combusted with a sample oxidizer (306, Packard, USA). Aliquots of urine and bile (ca. 0.2ml) were mixed with EMULSIFIER SCINTILLATOR[®] (Packard, USA). The radioactivities of all samples were determined using a liquid scintillation spectrometer (TRI-CARB 4640, Packard, USA).

Results

Serum Radioactivity Level

1. Single Dose

Serum levels of radioactivity after single oral or intravenous administration of ¹⁴C-SM-10888 (5mg/kg) under non-fasted conditions are shown in Fig. 2. Following oral administration, the level reached a maximum (C_{max} 1.09 μ g eq./ml) at 30min, and thereafter declined with a half-life of ca. 10hr. The AUC_{0-72} (calculated with trapezoidal rule, same hereafter) was 18.6 μ g eq.hr/ml. After intravenous administration, the serum level was 5.50 μ g eq./ml at 5min, followed by a biphasic decline with half-lives of ca. 3hr (to 24hr) and ca. 13hr (from 24 to 72hr). The AUC_{0-72} for i.v. was 20.8 μ g eq.hr/ml, giving a

Fig. 2 Serum levels of radioactivity in rats after single oral or intravenous administration of ¹⁴C-SM-10888 at dose of 5 mg/kg. Each point represents the mean $\pm$ S.E. of 5 rats.

Fig. 3 Serum levels of radioactivity in rats after single oral administration of ¹⁴C-SM-10888 at dose of 5 mg/kg under fasted or non-fasted conditions. Each point represents the mean $\pm$ S.E. of 5 rats.

Fig. 4 Serum levels of radioactivity in rats after single oral administration of ^{14}C -SM-10888 at doses of 1, 5 and 20 mg/kg. Each point represents the mean $\pm$ S.E. of 5 rats.

Fig. 5 Serum levels of radioactivity in rats during repeated daily administration of ^{14}C -SM-10888 at dose 5 mg/kg/day. Each point represents the mean $\pm$ S.E. of 5 rats.

Table 1 Tissue levels of radioactivity in rats after single oral administration of ^{14}C -SM-10888 at dose of 5 mg/kg

Tissue	Concentration ($\mu\text{g eq./g tissue}$)		
	0.5 hr ^{a)}	2 hr	24 hr
Cerebrum	1.40 $\pm$ 0.31 ^{b)}	0.88 $\pm$ 0.22	<0.01
Cerebellum	1.17 $\pm$ 0.25	0.77 $\pm$ 0.18	<0.01
Thyroid	0.95 $\pm$ 0.30	0.53 $\pm$ 0.17	<0.08
Salivary gland	3.62 $\pm$ 0.61	4.34 $\pm$ 0.96	0.38 $\pm$ 0.20
Thymus	1.17 $\pm$ 0.32	0.80 $\pm$ 0.22	<0.01
Heart	0.91 $\pm$ 0.22	0.59 $\pm$ 0.12	0.02 $\pm$ 0.00
Lung	1.41 $\pm$ 0.31	1.00 $\pm$ 0.28	0.07 $\pm$ 0.01
Liver	5.07 $\pm$ 0.78	3.12 $\pm$ 0.74	1.22 $\pm$ 0.05
Stomach	8.16 $\pm$ 2.18	2.93 $\pm$ 0.74	0.03 $\pm$ 0.01
Large intestine	1.25 $\pm$ 0.37	0.90 $\pm$ 0.25	0.52 $\pm$ 0.09
Small intestine	7.17 $\pm$ 1.59	4.18 $\pm$ 1.22	0.24 $\pm$ 0.04
Pancreas	1.96 $\pm$ 0.39	1.20 $\pm$ 0.31	0.02 $\pm$ 0.01
Spleen	2.14 $\pm$ 0.48	1.20 $\pm$ 0.35	0.01 $\pm$ 0.00
Adrenal	3.57 $\pm$ 0.35	2.05 $\pm$ 0.54	0.10 $\pm$ 0.01
Kidney	4.08 $\pm$ 0.63	3.02 $\pm$ 0.96	0.32 $\pm$ 0.02
Bladder	2.63 $\pm$ 0.11	1.58 $\pm$ 0.67	0.13 $\pm$ 0.04
Testis	1.05 $\pm$ 0.29	0.76 $\pm$ 0.19	<0.01
Bone marrow	1.78 $\pm$ 0.48	1.11 $\pm$ 0.23	<0.03
Fat	0.95 $\pm$ 0.21	0.57 $\pm$ 0.29	<0.02
Muscle	0.65 $\pm$ 0.20	0.46 $\pm$ 0.12	<0.01
Skin	0.82 $\pm$ 0.23	0.59 $\pm$ 0.14	0.08 $\pm$ 0.01
Blood	0.61 $\pm$ 0.16	0.47 $\pm$ 0.10	0.04 $\pm$ 0.00
Serum	0.82 $\pm$ 0.21	0.60 $\pm$ 0.11	0.04 $\pm$ 0.01

a) Time after administration

b) Mean $\pm$ S.E. of 3 rats

p.o./i.v. ratio of 89.4%.

Serum levels of radioactivity after single oral administration of ^{14}C -SM-10888 (5mg/kg) under non-fasted or fasted conditions are shown in Fig. 3. In rats fasted for 24hr before dosing, $C_{\max}$ was 2.52 $\mu\text{g eq./ml}$ at 1hr, and the level declined with a half-life of ca. 4hr. The AUC_{0-72} value was 22.5 $\mu\text{g eq.hr/ml}$.

Serum levels of radioactivity after single oral administrations of ^{14}C -SM-10888 at doses of 1, 5 and 20mg/kg are shown in Fig. 4. In rats receiving 1mg/kg, $C_{\max}$ was 0.21 $\mu\text{g eq./ml}$ at 1hr, and the same level was maintained until the 4hr time point (0.21 $\mu\text{g eq./ml}$), followed by decline with a half-life of ca. 8hr. The AUC_{0-72} was 3.2 $\mu\text{g eq.hr/ml}$. In rats receiving 20mg/kg, the serum level was 3.45 $\mu\text{g eq./ml}$ at 2hr, and this was maintained until 6hr (3.72 $\mu\text{g eq./ml}$), subsequently declining with a half life of ca. 11hr. The AUC_{0-72} was 112 $\mu\text{g eq.hr/ml}$.

2. Repeated Dose

Serum levels of radioactivity after repeated oral administration of ^{14}C -SM-10888 at dose of 5mg/kg/day are shown in Fig. 5. At day 1, the serum level peaked at 30min (0.81 μg

Fig. 6 Cumulative excretion of radioactivity into the urine and feces after single oral administration of ^{14}C -SM-10888 at dose of 5mg/kg to male rats. Each point represents the mean $\pm$ S.E. of 5 rats.

eq./ml), declined slightly by 6hr, and then fell to $0.12\mu\text{g eq./ml}$ by 24hr. From days 2 to 13, the serum levels at 30min and 24hr after every daily dose were ca. $1.0\mu\text{g eq./ml}$ and ca. $0.1\mu\text{g eq./ml}$, respectively, so that the pattern of changes in serum levels was quite steady throughout. At day 14, the level reached a maximum (C_{max}) of $0.73\mu\text{g eq./ml}$ at 30min, remained almost consistent until 6hr, and then declined to $0.26\mu\text{g eq./ml}$ at 24hr.

Biodistribution

1. Single Dose

Table I summarizes the tissue levels of radioactivity at 30min, 2 and 24hr after single oral administration of 5mg/kg of ^{14}C -SM-10888.

At 30min, in all tissues except the muscle, radioactivity level was equal to or exceeded the serum level ($0.82\mu\text{g eq./g}$). The gastrointestinal (GI) tract (e.g. the stomach ($8.16\mu\text{g eq./g}$) and the small intestine ($7.17\mu\text{g eq./g}$)) exhibited the highest level of radioactivity, followed by the liver ($5.07\mu\text{g eq./g}$), the kidney ($4.08\mu\text{g eq./g}$), the salivary gland ($3.62\mu\text{g eq./g}$) and the adrenal ($3.57\mu\text{g eq./g}$). In the cerebrum, the target organ of SM-10888, the level ($1.40\mu\text{g eq./g}$) exceeded that in the serum ($0.82\mu\text{g eq./g}$).

At 2hr, the levels in most of the tissues except the salivary gland had decreased in comparison to those at 30min. The salivary gland showed the highest radioactivity, fol-

Table II Tissue levels of radioactivity in rats after repeated daily administration of ^{14}C -SM-10888 at dose of 5 mg/kg/day

Tissue	Concentration ($\mu\text{g eq./g tissue}$)			
	0.5 hr ^{a)}	2 hr	24 hr	72 hr
Cerebrum	1.27 $\pm$ 0.13 ^{b)}	1.70 $\pm$ 0.21	N.D. ^{c)}	N.D. ^{c)}
Cerebellum	1.17 $\pm$ 0.16	1.41 $\pm$ 0.18	N.D. ^{c)}	N.D. ^{c)}
Pituitary	2.32 $\pm$ 0.28	3.92 $\pm$ 0.62	N.D. ^{c)}	N.D. ^{c)}
Thyroid	1.55 $\pm$ 0.59	1.76 $\pm$ 0.32	N.D. ^{c)}	N.D. ^{c)}
Salivary gland	4.37 $\pm$ 0.65	13.24 $\pm$ 1.66	0.17 $\pm$ 0.03	N.D. ^{c)}
Thymus	1.13 $\pm$ 0.11	1.59 $\pm$ 0.05	N.D. ^{c)}	N.D. ^{c)}
Heart	0.91 $\pm$ 0.15	1.37 $\pm$ 0.13	0.07 $\pm$ 0.01	N.D. ^{c)}
Lung	1.58 $\pm$ 0.15	2.39 $\pm$ 0.41	0.25 $\pm$ 0.04	0.17 $\pm$ 0.01
Liver	4.09 $\pm$ 0.38	12.60 $\pm$ 0.89	5.24 $\pm$ 0.49	2.17 $\pm$ 0.05
Stomach	11.00 $\pm$ 1.55	6.05 $\pm$ 1.25	0.27 $\pm$ 0.12	N.D. ^{c)}
Large intestine	2.30 $\pm$ 0.39	3.35 $\pm$ 0.40	0.67 $\pm$ 0.22	N.D. ^{c)}
Small intestine	10.59 $\pm$ 3.93	10.40 $\pm$ 2.81	0.88 $\pm$ 0.27	N.D. ^{c)}
Pancreas	1.50 $\pm$ 0.39	2.40 $\pm$ 0.39	0.05 $\pm$ 0.01	N.D. ^{c)}
Spleen	2.19 $\pm$ 0.55	3.20 $\pm$ 0.43	0.10 $\pm$ 0.02	0.10 $\pm$ 0.01
Adrenal	3.03 $\pm$ 0.72	4.85 $\pm$ 0.67*	0.40 $\pm$ 0.04	0.20 $\pm$ 0.01
Kidney	4.62 $\pm$ 1.02	6.90 $\pm$ 0.74	0.98 $\pm$ 0.06	0.38 $\pm$ 0.02
Bladder	3.26 $\pm$ 1.68	2.72 $\pm$ 0.43	0.29 $\pm$ 0.05	0.14 $\pm$ 0.01
Prostate	1.66 $\pm$ 0.68	1.81 $\pm$ 0.24	0.08 $\pm$ 0.01	N.D. ^{c)}
Testis	0.76 $\pm$ 0.20	1.54 $\pm$ 0.21	N.D. ^{c)}	N.D. ^{c)}
Bone marrow	1.85 $\pm$ 0.57	2.55 $\pm$ 0.31	N.D. ^{c)}	N.D. ^{c)}
Fat	0.57 $\pm$ 0.13	1.48 $\pm$ 0.26	N.D. ^{c)}	N.D. ^{c)}
Muscle	0.65 $\pm$ 0.18	0.98 $\pm$ 0.15	N.D. ^{c)}	N.D. ^{c)}
Skin	1.07 $\pm$ 0.12	1.17 $\pm$ 0.12	0.23 $\pm$ 0.06	0.16 $\pm$ 0.02
Blood	0.66 $\pm$ 0.11	0.96 $\pm$ 0.09	0.26 $\pm$ 0.05	0.22 $\pm$ 0.02
Serum	0.64 $\pm$ 0.15	1.03 $\pm$ 0.11	0.12 $\pm$ 0.02	N.D. ^{c)}

a) Time after administration

b) Mean $\pm$ S.E. of 5 rats (*: Mean $\pm$ S.E. of 4 rats)c) Not detected (<0.05)

lowed by the small intestine (4.18 $\mu\text{g eq./g}$), the liver (3.12 $\mu\text{g eq./g}$), the kidney (3.02 $\mu\text{g eq./g}$), the stomach (2.93 $\mu\text{g eq./g}$) and the adrenal (2.05 $\mu\text{g eq./g}$). At 24hr, the levels in the liver (1.22 $\mu\text{g eq./g}$), the large intestine (0.52 $\mu\text{g eq./g}$), the salivary gland (0.38 $\mu\text{g eq./g}$) and the kidney (0.32 $\mu\text{g eq./g}$) were relatively higher than those in the rest of the tissues, which were similar to the serum level (0.04 $\mu\text{g eq./g}$) or below the detection limit.

2. Repeated Dose

Rats received repeated oral doses (5mg/kg/day) of ^{14}C -SM-10888 for 14 days, and the tissue radioactivity levels at 30min, 2, 24 and 72hr after the final dose are summarized in Table II.

At 30min after the final dose, radioactivity was distributed throughout the body, all tissues demonstrating levels almost identical to or exceeding the serum level (0.64 $\mu\text{g eq./g}$). In particular, the stomach (11.00 $\mu\text{g eq./g}$), the small intestine (10.59 $\mu\text{g eq./g}$)

Fig. 7 Cumulative excretion of radioactivity during repeated daily administration of ^{14}C -SM-10888 at dose of 5mg/kg/day to male rats. Each point represents the mean $\pm$ S.E. of 5 rats.

Fig. 8 Cumulative excretion of radioactivity into the bile, urine and feces after single oral administration of ^{14}C -SM-10888 at dose of 5mg/kg to male rats. Each point represents the mean $\pm$ S.E. of 5 rats.

and the liver ($10.00\mu\text{g eq./g}$) showed high levels, followed by the salivary gland ($6.87\mu\text{g eq./g}$), the kidney ($4.62\mu\text{g eq./g}$), the bladder ($3.26\mu\text{g eq./g}$) and the adrenal ($3.03\mu\text{g eq./g}$).

At 2hr after the final dose, as compared to the 30min time point, the levels in all tissues but the stomach ($6.05\mu\text{g eq./g}$) and the small intestine ($10.40\mu\text{g eq./g}$) had increased along with the serum level ($1.03\mu\text{g eq./g}$). The levels in the salivary gland ($13.24\mu\text{g eq./g}$), the liver ($12.60\mu\text{g eq./g}$), the small intestine ($10.40\mu\text{g eq./g}$), the kidney ($6.90\mu\text{g eq./g}$), the stomach ($6.05\mu\text{g eq./g}$) and the adrenal ($4.85\mu\text{g eq./g}$) were especially elevated.

At 24hr, the levels in all tissues were lower than those at 2hr. That in the liver was still relatively high, but the concentration in the salivary gland was as low as the serum level ($0.12\mu\text{g eq./g}$).

At 72hr, except for the liver ($2.17\mu\text{g eq./g}$) and the kidney ($0.38\mu\text{g eq./g}$), the activities in most of tissues were around or below the detection limit.

Excretion

1. Urine and Feces

Cumulative excretion of radioactivity into the urine and feces after single oral administration of ^{14}C -SM-10888 at dose of 5mg/kg are shown in Fig. 6. Excretion was almost completed at 24hr post dosing (urine ; 45.8%, feces ; 33.2%), and at 168hr 52.2% of dose

had been excreted into the urine, and 44.2% into feces, i.e. total recovery was 96.4%. No radioactivity was found in the expired air.

Cumulative excretion of radioactivity relative to cumulative dose during repeated daily oral administration of ^{14}C -SM-10888 at dose of 5mg/kg/day is shown in Fig. 7. The excretion pattern remained essentially consistent from day 4 (urine ; 38.3%, feces ; 46.3%, total ; 84.6%) to day 14 (urine ; 42.8%, feces ; 47.5%, total ; 90.3%). At 72hr after the final dose, total radioactivity excreted was 48.3% into the urine and 43.7% into the feces (total 92.0%).

2. Bile

Bile-duct annulated rats received 5mg/kg of ^{14}C -SM-10888 orally, and the cumulative excretion of radioactivity into bile, urine and feces is shown in Fig. 8. Excretion of radioactivity was almost complete at 24hr post dosing (bile ; 63.8%, urine ; 27.9%, feces ; 0.8%). At 72hr recovery was 65.1% in bile, 29.1% in urine and 1.3% in feces.

Discussion

In order to clarify the disposition of SM-10888, ^{14}C -labeled compound was given to rats, either orally or intravenously, and its absorption, distribution and excretion were investigated.

Since after oral dosing of ^{14}C -SM-10888 at 5mg/kg, the serum peak level of radioactivity was observed at 30min, and the AUC value was almost equal to that for intravenous application, rapid and high absorption of the compound from the GI tract is indicated.

To examine the effect of diet on absorption, serum levels of radioactivity were compared between fasted and non-fasted conditions. Although AUC did not markedly differ, $C_{\max}$ in fasted rats was 2-fold higher than in non-fasted animals, suggesting that the absorption from the GI tract was delayed by the presence of food.

When rats were administered 1, 5 and 20mg/kg of ^{14}C -SM-10888, $C_{\max}$ and AUC increased in direct proportion to the dose level indicating no alteration in absorption characteristics within the range of doses tested.

Serum levels of radioactivity during repeated daily dosing were essentially identical to those after single dose and a steady state was maintained throughout two weeks of application. Repeated dosing would therefore be expected to exert minimal effects on disposition.

When ^{14}C -SM-10888 was given to rats orally, radioactivity was distributed throughout the body, including the cerebrum, the target organ of the drug, and then declined along with elimination from serum. No significant accumulations were evident and since SM-10888 is a lipophilic compound with a octanol/buffer (pH7.4) partition coefficient ($\log P^* = 2.23^5$), this might result in high membrane permeability and a widespread distribution pattern. Although tissue levels of radioactivity after repeated dosing were 1 to 4-fold higher than those after single dose, they also declined in line with reduction in the serum level.

Rat excreted almost all the radioactivity given orally into the urine and feces even with repeated dosing. The biliary excretion study confirmed that most of the radioactivity in

the feces can be attributed to biliary excretion. The sum of the excretion rates into the bile and urine (94% at 72hr) also provides further support for a high absorption rate of this compound from the GI tract.

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