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Distribution and Excretion of Thallium after Oral and Intraperitoneal Administration of Thallous Malonate and Thallous Sulfate in Hamsters

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Thallium compounds have been used medicinally as a depilatory as well as in suicides and murders. As a consequence, there have been many cases of thallium poisoning (Gastel 1978; Thompson 1981). These compounds are used as rodenticides and insecticides in some countries (Saddique & Peterson 1983; Kazantzis 1986). Recently, with changes in the industrial structure, new organic thallium compounds are being investigated (Kusumegi 1985). Although numerous investigators have reported on aspects of production, there have been few reports on toxicity and biological effect. In 1985, we reported acute poisoning by intentional ingestion of thallous malonate, an intoxication that was different from inorganic thallium intoxication (Aoyama et al. 1986). The distribution of thallium in this case was different from previous human and animal cases, with the thallium concentration in heart higher than that in kidney.

The present study investigated distribution and elimination patterns in an animal experiment in order to evaluate the toxicity of thallous malonate in comparison with that of thallous sulfate.

MATERIALS AND METHODS

Male Syrian golden hamsters, weighing 97±5g, were obtained from the Shizuoka Agricultural Cooperative Association for Laboratory Animals, Japan. The animals had free access to a pellet feed manufactured by CLEA Japan, Inc., and distilled water. They were housed at 20-25^{o}C.

Thallous malonate (Soekawa Chemical Co., Ltd., Japan; 99.9%) and thallous sulfate (Mitsuwa Chemical Co., Ltd., Japan; 99.9%) were dissolved in distilled water. The animals were fasted 12 h before treatment. The 65

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animals were divided into three groups: 5 animals received 0.5 ml of distilled water as control group; a single oral dose of 12.5 mg/kg body weight of thallous malonate was administered to 25 animals and the same intraperitoneal dose to 5 animals; and 25 animals received a single oral dose of 12.35 mg/kg body weight of thallous sulfate and the same intraperitoneal dose to 5 animals. These doses were administered in 0.5 ml water on day 0 by gastric intubation or injection. Animals were killed at 1, 12, 24, 72 and 168 hr after administration. Blood and organs from each group were taken for thallium analysis. Five hamsters were housed in plastic metabolic cages and urine and feces were collected separately each day for analysis. All materials were preserved frozen at -20°C until assay.

Organs washed with saline were digested. Feces were soluble in distilled water. A portion of each sample, 1-2 g of organ or 1 ml of blood or urine, was put into a test tube with 5 ml of mixed acid (16 N nitric acid and perchloric acid, Wako Pure Chemical Industries, Ltd., Tokyo; analytical grade). The test tubes were heated in a heating block (HF-61, Yamato Scientific Industries, Ltd., Tokyo) at 100°C for 60 min, then at 130°C for 60 min. The digests were adjusted to pH 8.5-9.0 with 25% (v/v) ammonia/water (Wako; analytical grade), and 2 ml of sodium diethyldithio-carbamate (Wako; analytical grade) and 10 ml of water-saturated methyl isobutyl ketone (Kanto Chemical Co., Tokyo) were added. After 15 min of shaking in a KM SHAKER (CV-D, IWAKI Co.,Ltd., Tokyo), the solution was centrifuged at 800 x g for 2 min. Thallium concentration in the organic phase was measured with an atomic absorption spectrophotometer (model A-640, Shimadzu, Ltd., Japan) in an acetylene/air flame with D_2 lamp correction (Wall 1977). The detection limit of thallium measured by this method is 0.1 µg/ml. The mean of the coefficient of variation of our analyses was 4%.

The elimination rates for thallium from various tissues were computed using a suitable pharmacokinetic program (Talas 1983). The rates from kidney, heart, liver and whole blood were estimated by fitting the data from t=1 (hour) to t=168 (hour) to a theoretical equation with two exponential terms. Then two half lives corresponding to the two exponential term, the α-phase and β-phase half lives, were computed. The half lives from brain, testis and muscle were computed using a single exponential function taking the data from t=12 (hours) to t=168 (hours) for brain, and the data from t=24 (hours) to t=168 (hours) for testis and muscle. Both urinary and fecal excretion rate constants (Kex) were also computed assuming one-compartment model for their excretion mechanism (Yamaoka 1984).

Table 1. Distribution of thallium in organs after the oral administration of thallous malonate and thallous sulfate.

Organs	Compounds	Concentrations of thallium (μg Tl/g wet wt.)				
		Hours after administration				
		1	12	24	72	168
Brain	Tl-M[a]	0.6±0.1[d]	3.2±0.7	3.0±0.3	1.7±0.8	0.7±0.2
	Tl-S[b]	n.d.	3.9±0.3	3.7±0.3	2.2±0.3	1.3±0.1
Heart	Tl-M	21.0±3.4[d]	9.4±1.3	6.6±0.7	3.9±0.4	1.5±0.5
	Tl-S	11.4±1.7	9.9±1.0	7.2±0.7	4.1±0.4	3.0±0.4
Liver	Tl-M	39.7±6.2	8.0±0.6	5.8±0.4	4.3±0.4	2.0±0.4
	Tl-S	14.3±7.6	7.8±2.4	6.6±2.1	3.3±0.8	3.0±0.4
Kidney	Tl-M	88.4±21.8[c]	97.6±6.2[d]	41.5±0.9	25.9±4.3	15.2±7.2
	Tl-S	58.5±8.4	70.5±12.0	51.3±14.0	25.7±4.7	16.4±2.2
Testis	Tl-M	1.0±0.1[d]	5.8±0.1[c]	14.0±1.0	10.8±0.8	10.5±0.4
	Tl-S	n.d.	12.9±1.8	14.7±0.7	13.1±1.7	7.6±0.9
Muscle	Tl-M	1.2±0.5[c]	6.8±2.5	9.1±1.2	7.0±0.6	2.2±0.5[d]
	Tl-S	n.d.	9.0±0.1	9.1±2.4	8.2±1.0	4.2±0.6
Whole blood	Tl-M	1.7±0.6	1.2±0.2	0.8±0.1[d]	0.4±0.1[c]	n.d.
	Tl-S	1.5±0.6	1.2±0.1	1.0±0.1	0.5±0.1	n.d.

Values are mean ± standard deviation for five animals. n.d. means below 0.1μg/g. [a]=thallous malonate. [b]=thallous sulfate. [c]=Significantly different from the group of thallous sulfate, $P<0.05$. [d]=Significantly different from the group of thallous sulfate, $p<0.01$.

The data were analyzed statistically using Student's t test. Significant differences between the means of the treated and control groups and the P values were calculated.

RESULTS & DISCUSSION

Table 1 shows the distribution of thallium in tissues after the oral administration of thallous malonate and thallous sulfate. Thallium was not detected in tissues from the group which was administered distilled water.

By 1 h after administration of thallous malonate, thallium was detected in all organs. On the contrary, thallium was only detected in the heart, liver and kidney in the group given thallous sulfate. By 12 h, the maximum values (except for muscle and

Table 2. The half lives in tissues after oral administration of thallous malonate and thallous sulfate.

Tissues	Half lives in tissues (hours)[a]	
	Thallous malonate	Thallous sulfate
Brain	68.9	93.9
Muscle	77.1	124.0
Testis	415.1	156.2

Tissues	Half lives in tissues (hours)[b]			
	Thallous malonate		Thallous sulfate	
	α-phase	β-phase	α-phase	β-phase
Heart	4.8	60.8	20.1	309.4
Liver	2.8	91.9	11.7	303.7
Kidney	12.1	207.4	24.2	95.6
Whole blood	11.0	89.6	15.0	55.7

[a]=Calculated with the open single compartment model.
[b]=Calculated with the open two compartment model.

testis) were observed in both treated groups and the distribution patterns were similar. At this point, although the thallium concentration in the brain was less than in other organs, thallium was rapidly deposited in the brain in both treated groups.

Table 2 shows the half lives from tissues after oral administration of thallous malonate and thallous sulfate. The heart, liver, kidney and whole blood had short half lives in the α phase. But the β phase in these tissues and in brain, muscle and testis had long half lives. These data indicated that thallium disappeared slowly from organs.

Figure 1 shows the cumulative elimination of thallium after the oral and intraperitoneal administration of thallous malonate and thallous sulfate. No thallium was detected in the urine or feces over a three day period prior to administration of the thallium compounds. In the group treated orally with thallous malonate, the urinary elimination rate constant was 0.175 (day^{-1}), the fecal rate was 0.500. In the group treated intraperitoneally with thallous malonate, the urinary elimination rate constant was 0.086, the fecal rate was 0.081. In the group treated orally with thallous sulfate, the urinary elimination rate constant was

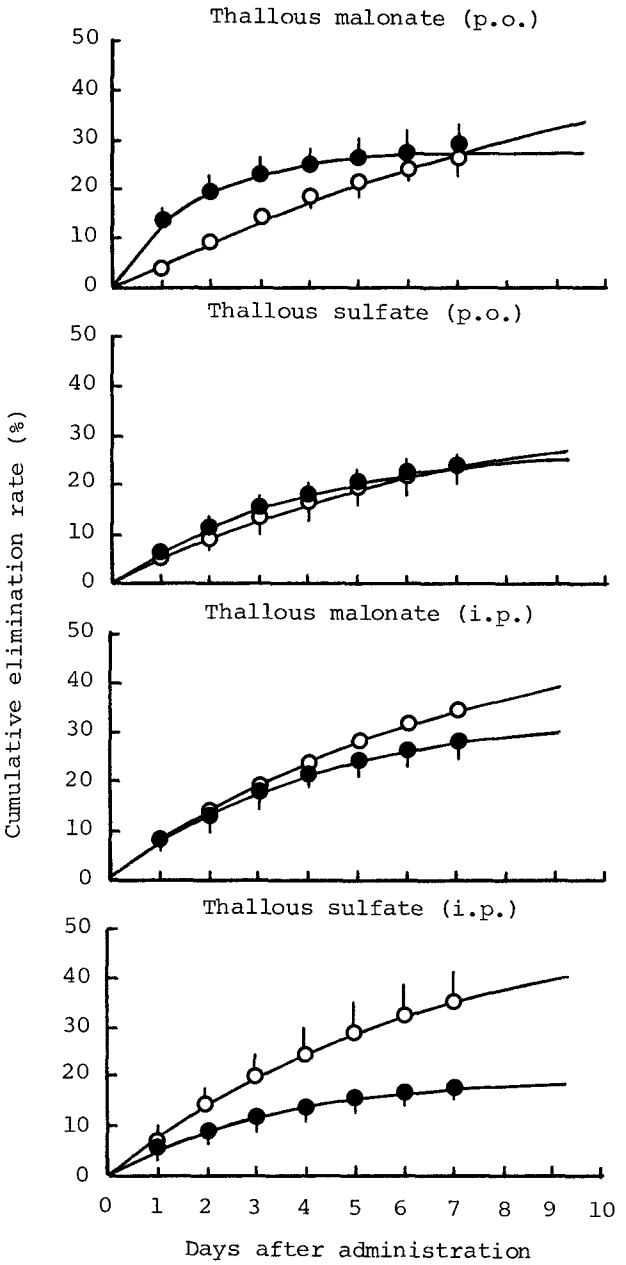

Figure 1. Cumulative elimination of thallium after the oral and intraperitoneal administration of thallous malonate and thallous sulfate. Dots with vertical lines represent mean ± standard deviation from five hamsters. (urine, ● ; feces, ○).

0.073, the fecal rate was 0.054. In the group treated intraperitoneally with thallous sulfate, the urinary elimination rate was 0.063, the fecal rate was 0.084. Compared with the group treated with thallous malonate and thallous sulfate, the former group was more rapidly eliminated from urine and feces than the latter. Among four treated groups the total elimination rate was about 50-60% and the values were low.

Generally thallium compounds are extremely toxic: the human lethal dose has been calculated to be about 10 to 15 mg/kg (Gastel 1978). In an animal experiment, the LD_{50} for rats given Tl_2SO_4, Tl_2CO_3 and TlCl were 23.5, 21.0 and 23.7 mg/kg, respectively (Tikhova 1964). There have been many reports concerning the toxicity of inorganic thallium compounds, but there have been few concerning organic thallium compounds. The LD_{50} (per os) of thallous malonate used in this study contained about 40 mg/kg as thallium (Aoyama et al. in press). A comparison of the toxicity of thallium compounds by means of LD_{50} revealed no remarkable differences between them. However, the animal species experiments which are necessary before drawing any final conclusions have yet to be performed. The values of the two thallium compounds used in this experiment (10 mg Tl/kg, 1/4 of LD_{50}) did not cause diarrhea, feces cruentae or body weight change in hamsters during the experiment. These findings showed that there were no differences in toxicity between the compounds.

In 1985, the author reported on the suicide of a researcher investigating its physio-chemical properties of thallous malonate (Aoyama et al. 1986). Immediately after oral intake, he developed acute renal failure, and in spite of two hemoperfusion treatments, died of cardiac failure. In autopsy, the thallium concentrations in his organs were different from those of inorganic thallium compounds. The heart (142 μg/g) had the highest concentration, followed by the ribs (137 μg/g), kidneys (119 μg/g), muscles (106 μg/g), testes (104 μg/g) and brain (83.9 μg/g). The thallium distribution pattern in this study differed from that of well-known inorganic thallium. The distribution pattern in hamsters treated with thallous malonate showed specific accumulation in the heart and testis. This pattern corresponded with the findings in the case of thallous malonate. In a study on the mechanism of Tl accumulation, Nakamura pointed out high Na^+,K^+-ATPase activity in heart and kidney; the mechanism of Tl accumulation in these organs is closely related to this activity (Nakamura et al. 1983). Namely, the thallium distribution pattern in this study may depend mainly on Na^+,K^+-ATPase in tissues.

Concerning testicular toxicity, Formigli et al. (1986)

reported spermatoxicity in rats repeatedly treated with thallous sulfate. Although spermatoxicity was not investigated in this study, the thallium concentration in testis in this experiment was similar to their results. It is thought that spermatoxicity will occur after a single oral administration of thallium.

Comparing thallous malonate and thallous sulfate from the perspective of chemical species, thallium was distributed more rapidly and at higher concentrations in the group given thallous malonate than that given thallous sulfate. This result was based on the difference in the absolute rate of the two thallium compounds. The results on distribution pattern are in agreement with those of Sabbioni (1980), who reported the distribution of di-methyl thallium. The results reported here indicate analogies in the distribution patterns of thallous malonate and thallous sulfate. It is considered that thallous malonate is decomposed into thallium ions and acts in this form in the body. The clarification of this problem will depend largely on future studies.

The total elimination rate of thallous malonate at 7 days was 55.2±5.3% in the orally administered group and 63.1±5.3% in the intraperitoneal group. The thallium elimination of both groups was relatively slow. In general, inorganic thallium compounds are deposited at a high level in the bone tissue (Talas & Wellhoner 1983). Thallium in organs at the 7th day ranged from 2/3 to 1/20 of the peak concentrations; yet a fair amount of thallium remained in organs at day 7. It was considered that the poor elimination rate in the group given thallous malonate implied high thallium affinity to hard and soft tissues.

There are large interspecies differences in the pattern of thallium excretion (Sabbioni & Manzo 1979). The elimination route changed with time after the oral administration of thallous malonate: urinary elimination was the main route until day 2 ; after day 3 it changed to the fecal elimination. In the group given thallous malonate intraperitoneally, the fecal elimination rate was higher than the urinary elimination rate. This finding seems to indicate that the cause of the high fecal elimination rate was active thallium transport from serosa to mucosa.

From the facts described above, it may concluded that thallous malonate, an organic thallium compound, showed slightly higher elimination rate constant but similar toxicity and distribution pattern compared with thallous sulfate, an inorganic thallium compound.

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