Effects of Internal Exposure to $^{56}MnO_2$ Powder on Blood Parameters in Rats

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ABSTRACT

Objective: The pathological effects of internal exposure to manganese dioxide-56 ($^{56}MnO_2$) radioisotope particles have been previously examined in rats. Here we further examine the effects of $^{56}MnO_2$, focusing on changes in blood parameters.

Materials and Methods: Ten-week-old male Wistar rats were exposed to 3 doses of neutron-activated $^{56}MnO_2$ powder, nonradioactive MnO_2 powder, or external 60Co γ-rays (1 Gy, whole body). On days 3 and 61 postexposure, the animals were necropsied to measure organ weights and clinical blood parameters, including red blood cell and white blood cell counts; concentrations of calcium, phosphorus, potassium, and sodium; and levels of alanine aminotransferase (ALT), aspartate aminotransferase, amylase, creatinine, urea, total protein, albumin, triglycerides, high density lipoprotein, total cholesterol, and glucose.

Results: In the $^{56}MnO_2$-exposed animals, accumulated doses were found to be highest in the gastrointestinal tract, followed by the skin and lungs, with whole-body doses ranging from 41 to 100 mGy. There were no $^{56}MnO_2$ exposure-related changes in body weights or relative organ weights. The ALT level decreased on day 3 and then significantly increased on day 61 in the $^{56}MnO_2$-exposed groups. There were no exposure-related changes in any other blood parameters.

Conclusion: Although the internal doses were less than 100 mGy, internal exposure of $^{56}MnO_2$ powder showed significant biological impacts.

Keywords: Blood chemistry, internal radiation exposure, Mn-56, rats

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Introduction

After the atomic bombing of Hiroshima and Nagasaki, Japan, direct initial radiation from the explosions caused major biological effects. However, people who moved to these cities soon after the detonations who had not been exposed to the initial radiation were also reported to suffer from various syndromes similar to acute radiation effects [1]. It is possible they inhaled residual radioactive dust and were internally exposed, causing them to develop these disorders. One of the primary sources of residual radiation was manganese-56 (^{56}Mn), a radioisotope that had been produced in the soil by a neutron beam from the atomic bomb explosion [2]. We investigated the biological effects of ^{56}Mn to understand the significance of residual radiation.

We had previously studied Wistar rats exposed to neutron-activated manganese dioxide-56 ($^{56}MnO_2$) powder. Our dosimetry data had shown that the highest dose of internal irradiation from ^{56}Mn was in the gastrointestinal tract, with the next-highest doses in the lungs and skin [3]. There had been significant pathological changes in the small intestine and lungs despite a relatively low absorbed dose [4]. In our previous study, we could not assess the systemic effects of $^{56}MnO_2$ exposure, such as organ weights and clinical blood parameters, because the number of examined animals had been limited. A reduction in white blood cell (WBC) counts is a sensitive indicator of the acute effects of external radiation [5]. For investigating the biological effects of ionizing radiation, a number of studies have used clinical blood parameters, including alanine amino-transferase (ALT), aspartate amino-transferase (AST), creatinine, and urea levels, which are associated with hepatic and renal damage [6-13].

In this study, we focused on the effects of internal exposure to $^{56}MnO_2$ powder on body and organ weights and blood parameters. Three sets of $^{56}MnO_2$ powder with various specific radioactivities were prepared, and male Wister rats were exposed to the preparations. On postexposure days 3 and 61, the animals were necropsied. The collected blood samples were used to determine red blood cell (RBC) and WBC counts and calcium (Ca), phosphorus (P), potassium (K), sodium (Na), ALT, AST, amylase, creatinine, urea, protein, albumin, triglycerides, high density lipoprotein (HDL), total cholesterol, and glucose levels in sera.

This study aimed to investigate the effect of internal exposure to $^{56}MnO_2$ particles on basic biological parameters, including blood chemistry, and to assess possible systemic responses to this radioactive powder in rats.

Materials and Methods

MnO_2 powder

The MnO_2 powder was purchased from Rare Metallic Co. (Tokyo, Japan). Diameters of the particles ranged from 1 to 19 μm (40% of them were 5 μm or smaller in diameter). Details of the size distribution were described previously [3].

Animals

Ten-week-old male Wistar rats were purchased from the Kazakh Scientific Center of Quarantine and Zoonotic Diseases, Almaty, Kazakhstan. They were maintained with free access to basal diet and tap water. Animal rooms were maintained at 19°C-22°C with a relative humidity of 30%-70% and a 12h light cycle. Body weights were measured with an animal weighing scale (FX-2000; A&D Co., Tokyo, Japan) once a week during the experiment. Rats were divided into 6 groups: Mn56×1 (n=17), Mn56×2 (n=17), Mn56×3 (n=17), Co-60 (n=14), cold Mn (n=14), and control (n=14). The Mn56×1, Mn56×2, and Mn56×3 groups were exposed to 3 different activities of dispersed $^{56}MnO_2$ powder (100 mg) of 2.7×10^8, 5.5×10^8, and 8×10^8 Bq, respectively. The Co-60 group received 1 Gy of external ^{60}Co γ-ray whole-body irradiation. A total of 3 rats from each ^{56}Mn group were euthanized for dosimetry 0.5 h after exposure. From each group, 7 rats were euthanized on days 3 and 61 after exposure. The rats were placed in a box with isoflurane gas (Isoflurane; Fujifilm Wako Pure Chemical Corporation, Tokyo, Japan) for anesthesia and were euthanized by removing and collecting whole blood from an abdominal artery. The lungs, liver, heart, kidneys, spleen, testes, and seminal vesicles were dissected and weighed.

Irradiation and dosimetry of rat organs

Details of irradiation using $^{56}MnO_2$ powder and the corresponding method of internal dose estimation have been described previously [3]. In brief, $^{56}MnO_2$ was obtained by neutron activation using the Baikal-1 nuclear reactor at the National Nuclear Center, Kurchatov, Kazakhstan. Thermal neutron fluencies of 4×10^{14} n/cm^2, 8×10^{14} n/cm^2, and 1.2×10^{15} n/cm^2 were applied to each 100 mg of MnO_2 powder to produce $^{56}MnO_2$ with activities of 2.7×10^8 Bq /100 mg, 5.5×10^8 Bq /100 mg, and 8×10^8 Bq /100 mg for the Mn56×1, Mn56×2, and Mn56×3 groups, respectively. The basal level of 4×10^{14} n/cm^2 was chosen as the same neutron fluency found at the epicenter of the atomic bombing in Hiroshima [1]. Activated MnO_2 powder was sprayed into sealed boxes, which contained 8 or 9 rats per box. After 1 h, the rats were removed from the exposure boxes, housed in new cages, and allowed to cool down for 0.5 h. The animals were then euthanized. A sample of each organ was dissected and weighed. The ^{56}Mn radioactivity in each sample was measured with a γ-spectrometer. Absorbed fractions from β- and γ- irradiation in each organ, as well as that for the whole body, were calculated on the basis of the Monte Carlo code (version MCNP-4C) and the mathematical phantom of the rat. For cold Mn exposure, 100 mg MnO_2 powder without neutron activation was sprayed on the rats using the same exposure apparatus.

Whole-body γ-ray irradiation of 1 Gy was performed using a Teragam K-2 unit (UJP Praha, Praha-Zbraslav, Czech Republic). The rats were irradiated at 1 m distance from the ^{60}Co source at a dose rate of 1.0 Gy/min. At each irradiation, half of the radiation dose was administered from the top, and the other half was administered from the bottom. A radiophotoluminescence glass dosimeter (GD-302M; Chiyoda Technol Corporation, Tokyo, Japan), was used to estimate the ^{60}Co dose.

Blood parameters

After collecting whole blood, 0.3 mL was immediately transferred into a tube coated with ethylenediaminetetraacetic acid. It was diluted with saline for RBC counting or mixed with Turk's stain solution for WBC counting. A Burker-Turk counting chamber was used for cell counting. The remaining whole blood was transferred into serum separating tubes to obtain sera with centrifugation. Serum chemistries were measured using standard automated clinical chemistry analyzers at a clinical laboratory (INVIVO; Semey, Kazakhstan).

Statistical Analysis

All values are expressed as mean±standard error of the mean. For multiple comparisons, a one-way analysis of variance was applied after the equality of variances was checked by F-test. Thereafter, Tukey's honest significant difference test was performed to compare each treated group with the control group.

Results

Internal irradiation doses

Table 1 shows estimated accumulated doses of internal irradiation of ^{56}Mn in various organs in the 3 groups exposed to $^{56}MnO_2$ powder. Given 3 rats were randomly selected from each group for dosimetry, the remaining animals should have received these estimated radiation doses within the defined statistical deviation. The highest estimated irradiation doses were found in the colon: 290±61, 520±110, and 760±170 mGy in the Mn56×1, Mn56×2, and Mn56×3 groups, respectively. Similar doses were found in the ileum. The estimated doses in the stomach were approximately half of the ileum doses. The skin and the lungs also received elevated internal doses, although they were lower than those in the gastrointestinal tract. The estimated whole-body doses were 41±8 mGy, 91±3 mGy, and 100±10 mGy in the Mn56×1, Mn56×2 and Mn56×3 groups, respectively. The external irradiation dose from ^{60}Co exposure was 1 Gy.

Table 1. Accumulated doses of internal irradiation in individual organs of rats exposed to various doses of $^{56}MnO_2$

Organ	Mn56×1 (2.7×10^8Bq)	Mn56×2 (5.5×10^8Bq)	Mn56×3 (8×10^8Bq)
Trachea	5.8±2.4	12±0.2	19±3.7
Lung	25±3.7	48±9.0	65±13
Heart	1.1±0.2	3.9±0.9	8.3±1.2
Esophagus	6.9±1.2	16±3.5	25±5.6
Stomach	90±12	210±23	300±50
Ileum	170±24	420±7.1	610±140
Colon	290±61	520±110	760±170
Liver	1.5±0.3	4.5±0.9	7.1±1.6
Spleen	0.3±0.1	0.5±0.1	0.8±0.2
Kidney	0.3±0.1	0.6±0.1	1.0±0.2
Skin	71±23	110±2.3	140±2.8
Eyes	19±7.8	41±7.8	62±12
Whole Body	41±8.0	91±30	100±10

Each value shows mean±SEM (n=3, each group).

Body weight changes

The changes in body weight are shown in Figure 1. The initial average body weight was 254±5.5 g. Although the growth was temporarily disturbed for 3 days postexposure, it steadily increased afterward. There were no significant differences in average body weights among the groups from postexposure day 3 to day 61.

Organ weights

The relative weights of the lungs, liver, heart, kidneys, spleen, testis, and seminal vesicles on days 3 and 61 after exposure are summarized in Table 2. On day 3, there were no significant differences in any organ weight among the groups except spleen weights, which decreased in the Co-60 group. On day 61 after exposure, the lung weight decreased and the liver weight increased in the Mn56×1 group; however, these changes were not observed in the higher dose groups.

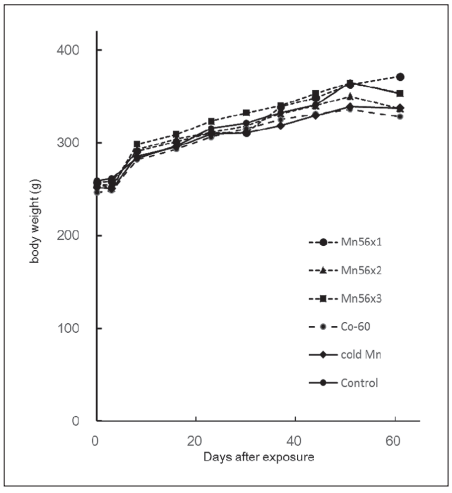

Figure 1. Changes in body weight after exposure. Ten-week-old male Wistar rats were exposed to 3 different activities of $^{56}MnO_2$ powder: Mn56×1 (circle/dotted line), Mn56×2 (triangle/dotted line), and Mn56×3 (square/dotted line); 1 Gy of whole-body ^{60}Co γ-ray irradiation: Co-60 (circle/broken line); cold MnO_2 powder: cold Mn (rhombus/straight line); or control (circle/straight line).

RBC and WBC counts

Table 3 summarizes RBC and WBC counts on days 3 and 61 postexposure in each group. There were no significant changes in RBC counts on either day 3 or day 61. WBC counts significantly decreased in the Co-60 group on day 3 after exposure, whereas no changes were observed in the Mn56 groups. On day 61, there were no significant differences in WBC counts among the groups.

Serum parameters

Serum chemistries, including serum ALT, AST, amylase, creatinine, and urea levels in each group, are summarized in Table 4. On day 3 postexposure, serum ALT levels decreased significantly in both the Mn56×3 and Co-60 groups. On day 61, however, it significantly increased in the Mn56×1 and Mn56×3 groups. Increases in amylase were noted in both the Mn56×1 and cold Mn groups. There were no changes in any other parameter, including serum Ca, P, K, Na, total protein, albumin, triglycerides, HDL, total cholesterol, and glucose levels, either on day 3 or day 61.

Discussion

To investigate the biological effects of internal exposure to $^{56}MnO_2$, we developed an experimental system to expose laboratory rats to $^{56}MnO_2$ powder [3]. Using this facility, we investigated, for the first time, the effects of $^{56}MnO_2$ on basic biological parameters, including body weight changes, organ weights, and blood chemistry, with a statistically significant number of rats. The same amount of MnO_2 with the same specific activity (2.7×10^8 Bq/100 mg) as our previous report was used in the Mn56×1 group, in which the estimated absorbed dose in each organ was comparable to that in our previous report, demonstrating the excellent reproducibility of our exposure system. For instance, the doses were 170 mGy in the ileum and 25 mGy in the lung in Mn56×1, and they were 150 mGy and 30 mGy, respectively, in our previous study. In the present study, $^{56}MnO_2$ with higher specific activities (5.4×10^8, and 8×10^8 Bq/100 mg) was also applied. As expected, doses in the organs were proportionally increased as the powder activity increased (Table 1).

Histological changes have been shown in rats exposed to $^{56}MnO_2$ powder [4]. The number of mitotic cells was increased in the small intestine, and hemorrhaging was found in the lungs after exposure. In this study, we explored whether any systemic changes resulted from internal exposure to $^{56}MnO_2$ powder, examining the effects on body weight changes, organ weights, and clinical blood parameters. Body weights did not increase for 3 days postexposure, probably because of the animals' stress from being brought to the facility for ^{56}Mn exposure, given all the groups showed a similar halt in body weight gain. However, the weights steadily increased thereafter without any significant differences between the groups. At necropsy on day 3 postexposure, there was a sig-

Table 2. Body and relative organ weights in rats exposed to $^{56}MnO_2$, Co-60 γ rays, and cold MnO_2

	Group	Body weight (g)	Lung (g/kg bw)	Liver (g/kg bw)	Heart (g/kg bw)	Kidney (g/kg bw)	Spleen (g/kg bw)	Testis (g/kg bw)	SV (g/kg bw)
Day 3	Mn56x1	234±11	5.6±0.4	28.4±1.0	3.8±0.2	8.1±0.2	3.8±0.3	11.7±0.6	3.4±0.5
	Mn56x2	237±12	6.3±0.5	28.1±0.8	3.5±0.1	8±0.3	3.9±0.3	11.3±0.6	4.6±0.6
	Mn56x3	245±16	5.7±0.2	29.2±0.5	3.6±0.2	7.8±0.2	4.2±0.2	12.2±0.6	3.7±0.8
	Co-60	234±14	5.6±0.4	29±1.5	3.5±0.1	8.1±0.3	3.1±0.2*	11.5±0.8	4.2±0.6
	Cold Mn	235±14	6.3±0.6	30.2±0.4	3.5±0.2	7.4±0.1	3.6±0.2	11.4±0.7	2.9±0.4
	Control	248±16	6±0.5	27.7±1.2	3.5±0.1	8.1±0.2	4.4±0.3	10.5±1.1	4±0.6
Day 61	Mn56x1	371±21	4.9±0.2*	35.7±1.4*	3.3±0.1	7.7±0.1	3.4±0.2	9.2±0.6	5.1±0.4
	Mn56x2	336±17	6±0.5	26.6±1.0	3.6±0.5	7.3±0.2	3.5±0.2	9.1±0.5	4±0.5
	Mn56x3	353±16	5.2±0.3	27±0.4	3±0.1	7.5±0.3	2.9±0.2	9.1±0.5	4±0.3
	Co-60	328±23	6.4±0.5	26.4±0.8	3.2±0.1	7.7±0.1	3.3±0.3	9.4±0.5	5±0.5
	Cold Mn	337±19	5.2±0.3	32.3±1.0	3.3±0.1	7.3±0.2	3.6±0.3	9.8±0.4	5±0.3
	Control	329±17	6.5±0.5	26.3±0.7	3.4±0.1	8.4±0.2	3.3±0.2	9.3±0.7	4.7±0.2

Each value shows mean±SEM (n=7, each group).
* indicates significantly different from each control by p<.05.

Table 3. RBC and WBC counts in rats exposed to $^{56}MnO_2$, Co-60 γ-rays, and cold MnO_2

	Group	RBC ($\times10^4$/μL)	WBC ($\times10^2$/μL)
Day 3	Mn56x1	880±25	56±6
	Mn56x2	833±43	44±8.7
	Mn56x3	783±71	58±4.5
	Co-60	827±23	20±4.6*
	Cold Mn	828±79	60±4.5
	Control	841±58	46±9.8
Day 61	Mn56x1	776±58	42±9.1
	Mn56x2	743±46	67±6.3
	Mn56x3	771±96	61±10.8
	Co-60	639±95	51±11.2
	Cold Mn	759±40	49±9.8
	Control	750±37	60±6.8

Each value shows mean±SEM (n=7, each group).
* indicates significantly different from each control by p<.05.
RBC: red blood cell; WBC: white blood cell

Table 4. Blood chemical parameters in rats exposed to $^{56}MnO_2$, Co-60 γ-rays and cold MnO_2

	Group	ALT (U/L)	AST (U/L)	Amylase (U/L)	Creatinine (umol/L)	Urea (mmol/L)
Day 3	Mn56x1	35±2.2	105±11.3	1797±88	30±2.0	5±0.40
	Mn56x2	33±1.5	90±3.9	1357±84	25±1.7	5.7±0.39
	Mn56x3	31±2.0*	103±8.2	1432±138	28±1.4	6.4±0.30
	Co-60	30±1.6*	89±9.4	1468±70	25±1.0	5.9±0.48
	Cold Mn	46±2.3	118±13.2	1942±133	27±1.5	5.6±0.57
	Control	40±2.8	107±10.7	1459±130	28±2.2	6.7±0.50
Day 61	Mn56x1	47±3.5*	97±11.7	2025±89*	27±1.3	5.7±0.36
	Mn56x2	43±3.3	77±6.1	1418±81	31±1.3	5.4±0.32
	Mn56x3	46±2.5*	85±5.1	1554±80	33±1.0	6.4±0.47
	Co-60	37±2.6	108±18.2	1319±203	30±2.8	5.5±0.39
	Cold Mn	42±3.0	113±19.3	2002±95*	27±0.5	5.4±0.51
	Control	36±1.9	84±7.2	1272±90	31±1.7	6±0.36

Each value shows mean±SEM (n=7, each group).
* indicates significantly different from each control by p<.05.
ALT: alanine aminotransferase; AST: aspartate amino-transferase

nificant reduction in WBC counts in the Co-60 group. Whole-body irradiation with over 0.4 Gy is known to reduce WBC counts, which maximally decrease on postirradiation days 1-3 and then gradually recover afterward [5]. WBC counts in the Co-60 group were indeed recovered on day 61. There were no effects on WBC counts in the Mn56 groups, suggesting that the hematopoietic system was not affected by the internal exposure to $^{56}MnO_2$ at the doses examined. RBCs are known to be resistant to radiation damage [5], which is consistent with our findings showing no changes in RBC counts in the present study. In addition, the relative spleen weight was reduced in the Co-60 group, which has also been previously established [12].

Blood clinical parameters have been used to evaluate the physiological changes caused by radiation exposure. In rats, whole-body γ-irradiation at over 3 Gy has been reported to increase serum ALT and AST levels; however the responses varied by experiment. Some studies have stated that serum ALT and AST levels were elevated a day after γ-irradiation [6, 11], whereas others had found that they initially decreased and then started to increase within 2 weeks of exposure [7, 8, 10]. Our results with Mn56 exposure were similar to the latter. Serum ALT levels decreased on postexposure day 3 and significantly increased on day 61 in the Mn56 groups. These reductions in serum ALT levels could be related to irradiation, but this change probably does not have clinical value, because ALT increases, not decreases, are an indicator of hepatic disorder or injury [6]. In contrast, significant increases in ALT levels on day 61 could indicate pathophysiological changes resulting from $^{56}MnO_2$ exposure. Although both ALT and AST are generally referred to as biomarkers for hepatic damage, AST is found in the heart, skeletal muscle, and liver and can represent acute hepatic damage [14]. The increases in ALT levels alone could indicate chronic changes in the liver. Further studies are required to understand the possible effects of $^{56}MnO_2$ exposure on hepatic pathology and function. High-dose-whole-body γ-irradiation can cause elevations in serum creatinine and urea levels [6, 7], which was not observed in the present study. Significant increases in serum amylase levels were noted in the cold Mn and Mn56×1 groups on day 61 but were not found in the higher dose groups, suggesting that the increase was not related to $^{56}MnO_2$ exposure.

Since ^{56}Mn emits both β particles and γ rays, the biological effects observed in our study may be due to β emission. Previous studies that compared rats exposed to the β-emitter, ^{144}Ce with those exposed to external X-ray irradiation showed comparable biological effects, while the α-emitter, ^{238}Pu, had 20 times higher effect [15,16]. The manner of internal exposure of certain radionuclides depends on its chemical nature [17-19]. Radiation doses were mainly found in the gastrointestinal tract, the lung, and the skin as expected since MnO_2 powder is stable and insoluble particles. It has been believed that irradiation from radioactive particles may be less hazardous than the same activity uniformly distributed [19]. However, our results showed that whole-body doses of less than 100 mGy from $^{56}MnO_2$ has a significant impact on blood parameters. Further studies are needed to understand the underlying mechanisms of the effects. It is well known that manganese is a neurotoxic chemical [20, 21]. Overexposure to manganese could induce symptoms similar to those of Parkinson's disease in humans as well as rodents. In the present study, no changes in behavior or any biological parameters were noted between the cold Mn group and control. Animals were exposed to MnO_2 powder for only 1 hour, which probably did not produce any chemical toxicity of Mn.

In case of an accident at a nuclear power plant or another facility dealing with radioactive materials, the general public can experience contamination from radioactive particles [22-24]. This study provides a tool to evaluate the effect of internal exposure to those radioactive particles in general, although ^{56}Mn itself is uncommon in the environment. Interestingly, ^{56}Mn had been found in the heads of medical linear accelerators after use, without causing any safety issues [25].

In conclusion, we investigated the effects of radiation exposure by $^{56}MnO_2$ powder on blood parameters in male Wistar rats over a period of 61 days. Although the absorbed internal doses of $^{56}MnO_2$ were relatively low, significant changes in serum ALT levels were observed. Our results suggest a potential biological impact of exposure to $^{56}MnO_2$ powder.

Ethics Committee Approval: Ethics committee approval was received for this study from the Animal Experiment Ethics Committee of Semey Medical University, Semey Kazakhstan.

Informed Consent: N/A.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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