Mobilization of Renal and Hepatic Cadmium by Dithiocarbamates in Rats

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Sodium *N*-benzyl-D-glucamine dithiocarbamate (BGD), sodium *N*-*p*-hydroxymethylbenzyl-D-glucamine dithiocarbamate (HBGD), sodium *N*-*p*-carboxybenzyl-D-glucamine dithiocarbamate (CBGD), and sodium *N*-*p*-methoxybenzyl-D-glucamine dithiocarbamate (MeOBGD) were evaluated for their efficacy in the distribution and excretion of cadmium in rats exposed to cadmium. Rats were injected intraperitoneally with $^{109}\text{CdCl}_2$ (1 mg Cd/kg and 74 kBq of ^{109}Cd /one animal) and 30 min or 24 h later, they were injected with chelating agents (400 $\mu\text{mol/kg}$). At both 30 min and 24 h after treatment with cadmium, these chelating agents all significantly enhanced the biliary excretion of cadmium. At 24 h after cadmium injection, BGD and MeOBGD were the most effective on the biliary excretion of the metal. These chelating agents were effective in mobilizing cadmium from the liver at 30 min after cadmium treatment. At 24 h after cadmium treatment, BGD and MeOBGD significantly depressed cadmium content in the liver. In another experiment, rats were injected intraperitoneally with $^{109}\text{CdCl}_2$ and 3 d later, they were injected with BGD, HBGD, or MeOBGD every other day for 2 weeks. The fecal excretion of cadmium was significantly increased by these chelating agents and MeOBGD was the most effective. The hepatic and renal cadmium contents were significantly decreased after BGD, HBGD or MeOBGD injection. The injection of MeOBGD to rats pretreated with cadmium was more effective than that of BGD, HBGD, or CBGD in removing cadmium from the liver. HBGD injection was more effective in decreasing the cadmium content in the kidney. The treatment with these chelating agents did not cause the redistribution of cadmium to brain, testes, and heart.

Keywords — cadmium; tissue distribution; excretion; sodium *N*-benzyl-D-glucamine dithiocarbamate; sodium *N*-*p*-hydroxymethylbenzyl-D-glucamine dithiocarbamate; sodium *N*-*p*-carboxybenzyl-D-glucamine dithiocarbamate; sodium *N*-*p*-methoxybenzyl-D-glucamine dithiocarbamate; chelating effect

Introduction

The administration of cadmium to animals results in a number of lesions in various organs, such as liver, kidney, and testes.¹⁻⁴ It is also known that kidney is the most sensitive organ to long-term exposure to cadmium, *i.e.*, the critical organ for this type of exposure.^{5,6} Therapeutic effects of various chelating agents in acute cadmium intoxication have been studied by many investigators. The injections of 2,3-dimercapto-1-propanol (BAL)⁷⁻¹¹ and dithiocarbamates¹²⁻¹⁶ to animals pretreated with cadmium 1 d to 3 weeks earlier, increased fecal excretion of cadmium and decreased hepat-

ic and renal cadmium burdens, but increased the cadmium load of brain, testes, and heart.¹²⁻¹⁴ We reported that the new dithiocarbamate derivatives, sodium *N*-benzyl-D-glucamine dithiocarbamate (BGD),¹⁷⁻¹⁹ sodium *N*-*p*-methylbenzyl-D-glucamine dithiocarbamate (MBGD),²⁰ and sodium *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate (PBGD),²⁰ were more effective than other dithiocarbamates in decreasing the cadmium concentrations in liver and kidney without redistribution of cadmium to the tissues, such as brain, testes, and heart. Jones *et al.*²¹ and Gale *et al.*^{22,23} reported that the injection of sodium *N*-*p*-methoxybenzyl-D-glucamine dithiocarbamate (MeOBGD) was

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more effective in decreasing the cadmium concentrations in the liver and kidney in cadmium pretreated mice than injection of BGD. Recently, we found that the injection of *N-p*-hydroxymethylbenzyl-D-glucamine dithiocarbamate (HBGD), which we synthesized recently, to mice pretreated with cadmium can remove cadmium from the body more effectively than injection of BGD or sodium *N-p*-carboxybenzyl-D-glucamine dithiocarbamate (CBGD).^{24,25)}

The present study was undertaken to further evaluate the comparative effects of BGD, HBGD, CBGD, and MeOBGD on the mobilization of renal and hepatic cadmium in rats exposed to cadmium.

Materials and Methods

Materials — $^{109}\text{CdCl}_2$ (specific activity, 58.2 GBq/mg) was obtained from New England Nuclear (Boston, MA). Cadmium chloride was obtained from Wako Pure Chemical Ind. (Osaka). The sodium salt of BGD was synthesized by the method of our previous paper.¹⁷⁾ The sodium salts of HBGD and CBGD were synthesized as described elsewhere.²⁶⁾ The sodium salt of MeOBGD was synthesized by the procedure of Jones *et al.*²¹⁾ Structures of the dithiocarbamates used are shown in Fig. 1. All other chemicals were of reagent grade.

R	abbreviation
$-\text{CH}_2-\text{C}_6\text{H}_5$	BGD
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2\text{OH}$	HBGD
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{COONa}$	CBGD
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{OCH}_3$	MeOBGD

Fig. 1. Structures of Dithiocarbamates Used

Excretion and Distribution of Cadmium after Single Injection of Chelating Agent — Male Wistar rats, weighing 180–200 g, were injected intraperitoneally with $^{109}\text{CdCl}_2$ (1 mg Cd/kg and 74 kBq of ^{109}Cd /one animal) and housed in intraperitoneally with $^{109}\text{CdCl}_2$ (1 mg Cd/kg and 74 kBq of ^{109}Cd /one animal) and housed in min or 24 h later the rats were anesthetized with urethane (1 g/kg, intraperitoneally). The bile duct was exposed through a midline abdominal incision and cannulated with a polyethylene tubing (PE 10). The rats were injected in-

TABLE I. Effects of Chelating Agents on Biliary and Urinary Excretion of Cadmium in Rats Pretreated with Cadmium, 30 min or 24 h Earlier

Chelating agent	Cadmium excreted/3 h (% of dose) ^{a)}			
	Cadmium pretreatment			
	30 min earlier		24 h earlier	
	Bile	Urine	Bile	Urine
Control	6.63 ± 1.37	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
BGD	39.52 ± 0.42 ^{b)}	0.23 ± 0.13 ^{b)}	11.45 ± 2.06 ^{b)}	0.29 ± 0.08 ^{b)}
HBGD	39.03 ± 3.98 ^{b)}	1.14 ± 0.35 ^{b,c)}	4.39 ± 1.16 ^{b,c)}	0.43 ± 0.06 ^{b,c)}
CBGD	25.13 ± 6.89 ^{b-d)}	1.20 ± 0.47 ^{b,c)}	2.43 ± 0.78 ^{b,c)}	0.29 ± 0.10 ^{b)}
MeOBGD	42.10 ± 1.90 ^{b,e)}	0.31 ± 0.05 ^{b,d,e)}	18.46 ± 4.56 ^{b,d,e)}	0.31 ± 0.10 ^{b)}

Rats were injected i.v. or i.p. with $^{109}\text{CdCl}_2$ (1 mg Cd/kg and 74 kBq ^{109}Cd /rat). Thirty minutes or 24 h later, they were injected i.p. with saline or chelating agents (400 $\mu\text{mol/kg}$) and then bile and urine samples were collected for 3 h. *a)* The values represent the mean ± S.D. for 5 animals. *b)* Significantly different from control at $p < 0.05$. *c)* Significantly different from BGD at $p < 0.05$. *d)* Significantly different from HBGD at $p < 0.05$. *e)* Significantly different from CBGD at $p < 0.05$.

traperitoneally with saline or a chelating agent (400 $\mu\text{mol/kg}$). Cadmium was injected intravenously when the chelating agents were administered 30 min after cadmium. Bile and urine samples were collected for an experimental period of 3 h. Then, the rats were killed with urethane and various tissues were collected. The levels of ^{109}Cd radioactivity in the bile, urine and tissues were determined using an Aloka auto-well gamma scintillation counter (model ARC 300).

Excretion and Distribution of Cadmium after 7 Injections of Chelating Agent — Male Wistar rats were injected intraperitoneally with $^{109}\text{CdCl}_2$ and housed in individual metabolic cages with drinking water and diet *ad libitum*. Three days later the rats were divided into 4 groups of 4 animals each, respectively, and given intraperitoneally with saline or a chelating agent (400 $\mu\text{mol/kg}$) every other day for 2 weeks. Each chelating agent was dissolved in 0.5 ml of saline and these solutions were prepared fresh every day. Fecal and urine samples were collected from each animal daily and were counted in the gamma counter for ^{109}Cd radioactivity. The rats were sacrificed by urethane anesthesia 48 h after the final administration and various tissues were removed for ^{109}Cd counting in the gamma counter.

Statistical Analysis — Data were analyzed

by a one-way analysis of variance. When the analysis indicated that a significant difference existed, the treated groups were compared to the controls by Duncan's new multiple range test. Since there were unequal variances in some of the data, it was necessary to use the non-parametric Kruska-Wallis test followed by the appropriate multiple comparison test.

Results and Discussion

Table I shows the biliary and urinary excretions of cadmium in rats when each chelating agent was injected 30 min after cadmium pretreatment. The major route of excretion of cadmium after injection of these chelating agents in cadmium-exposed rats was *via* the bile. Biliary excretion of cadmium was significantly increased by treatment with BGD, HBGD, CBGD, or MeOBGD. The cumulative biliary excretion of cadmium in a 3-h period after treatment with BGD, HBGD, or MeOBGD was significantly larger than that with CBGD. In addition, these chelating agents all significantly increased the urinary excretion of cadmium.

The tissue distribution of cadmium in rats at the end of the experiment is shown in Table II. The contents of cadmium deposited in the liver were significantly decreased by these chelating agents. Gale *et al.*^{13,14} reported that the injec-

TABLE II. Effects of Chelating Agents on Tissue Distribution of Cadmium in Rats Pretreated with Cadmium, 30 min or 24 h Earlier

Chelating agent	Cadmium (% of dose) ^{a)}			
	Cadmium pretreatment			
	30 min earlier		24 h earlier	
	Liver	Kidney	Liver	Kidney
Control	51.78 $\pm$ 5.10	1.49 $\pm$ 0.17	52.99 $\pm$ 5.05	2.07 $\pm$ 0.49
BGD	14.12 $\pm$ 3.08 ^{b)}	1.08 $\pm$ 0.03	42.70 $\pm$ 2.16 ^{b)}	1.88 $\pm$ 0.07
HBGD	18.52 $\pm$ 3.21 ^{b)}	1.20 $\pm$ 0.12	45.77 $\pm$ 6.18	1.96 $\pm$ 0.19
CBGD	25.43 $\pm$ 5.71 ^{b,c)}	1.48 $\pm$ 0.12	47.87 $\pm$ 1.74	2.30 $\pm$ 0.24
MeOBGD	14.81 $\pm$ 0.95 ^{b,d)}	1.19 $\pm$ 0.19	32.29 $\pm$ 6.03 ^{b-d)}	2.31 $\pm$ 0.06

Rats were injected i.v. or i.p. with $^{109}\text{CdCl}_2$ (1 mg Cd/kg and 74 kBq ^{109}Cd /rat). Thirty minutes or 24 h later, they were injected i.p. with saline or chelating agents (400 $\mu\text{mol/kg}$). At the end of the experiment, the rats were killed and the tissue distribution of cadmium was determined from radioactivity. a) The values represent the mean $\pm$ S.D. for 5 animals. b) Significantly different from control at $p < 0.05$. c) Significantly different from BGD at $p < 0.05$. d) Significantly different from HBGD at $p < 0.05$.

tions of dithiocarbamates, such as diethyldithiocarbamate and dimethyldithiocarbamate, to mice pretreated with cadmium caused the redistribution of cadmium to brain, testes, and heart. However, BGD, HBGD, CBGD, and MeOBGD did not cause the redistribution of cadmium to brain, testes, and heart (data not shown).

It has been reported that the induction of metallothionein synthesis within a few hours after cadmium exposure has a marked effect on the pharmacokinetics and toxicity of cadmium.²⁷⁾ Thus, we examined the comparative effects of these chelating agents on the biliary and urinary excretions of cadmium when administered 24 h after cadmium pretreatment, *i.e.*, after the synthesis of metallothionein (Table I). The biliary excretion of cadmium was significantly increased by treatment with BGD, HBGD, CBGD, or MeOBGD. BGD and MeOBGD showed the largest stimulatory effect on the biliary excretion of cadmium. In addition, these chelating agents increased the urinary excretion of cadmium to a small extent. The delayed treatment with these chelating agents showed less effectiveness on the biliary excretion of cadmium than that at 30 min after cadmium exposure.

Table II shows the tissue distribution of cadmium at 3 h after injection of the chelating agents into rats pretreated with cadmium 24 h

earlier. BGD and MeOBGD among these 4 chelating agents significantly reduced the contents of cadmium in the liver, the major site of accumulation of cadmium in the body. HBGD also tended to decrease the cadmium content in the liver. These results indicate that these chelating agents can mobilize metallothionein-bound cadmium from the rat body even after the synthesis of metallothionein, as reported in our previous papers.^{17,19)}

Furthermore, we investigated the comparative effects of repeated injections of the chelating agents other than CBGD, which had less effectiveness on the cadmium excretion in a single injection, on the fecal and urinary excretions of cadmium in rats pretreated with cadmium (Table III). The total fecal excretion of cadmium after BGD, HBGD, and MeOBGD treatment for the 2 weeks were, respectively, about 28, 24, and 37 times higher than that in the control. The increased fecal excretion of cadmium by MeOBGD was significantly larger than that by BGD or HBGD. The cumulative urinary excretion of cadmium was significantly increased by injections of these chelating agents and HBGD was the most effective. The major route of excretion of cadmium following injections of these chelating agents in cadmium-treated rats was the feces.

The results of the tissue distribution of cadmium in rats at the end of the experiment are

TABLE III. Cumulative Fecal and Urinary Excretion of Cadmium in Rats Pretreated with Cadmium and after Chelation Therapy

Chelating agent	Cadmium (% of dose) ^{a)}	
	Feces	Urine
Control	1.40 ± 0.13	0.02 ± 0.01
BGD	38.57 ± 4.47 ^{b)}	1.08 ± 0.12 ^{b)}
HBGD	33.13 ± 2.03 ^{b,c)}	2.68 ± 1.09 ^{b,c)}
MeOBGD	52.31 ± 6.32 ^{b-d)}	1.48 ± 0.41 ^{b)}

Rats were injected i.p. with ¹⁰⁹CdCl₂ (1 mg Cd/kg and 74 kBq ¹⁰⁹Cd/rat). Three days later they were injected i.p. with saline or chelating agents (400 μmol/kg) every other day for 2 weeks. Fecal and urine samples were collected in metabolic cages and counted for ¹⁰⁹Cd radioactivity. *a)* The values represent the mean ± S.D. for 5 animals. *b)* Significantly different from control at *p* < 0.05. *c)* Significantly different from BGD at *p* < 0.05. *d)* Significantly different from HBGD at *p* < 0.05.

TABLE IV. Effects of Chelating Agents on Tissue Distribution of Cadmium in Rats

Chelating agent	Cadmium (% of dose) ^{a)}	
	Liver	Kidney
Control	51.00 ± 1.56	5.12 ± 0.24
BGD	16.93 ± 4.19 ^{b)}	2.36 ± 0.14 ^{b)}
HBGD	18.86 ± 2.62 ^{b)}	1.81 ± 0.51 ^{b)}
MeOBGD	6.20 ± 0.36 ^{b-d)}	2.99 ± 0.36 ^{b,d)}

Rats were injected i.p. with ¹⁰⁹CdCl₂ (1 mg Cd/kg and 74 kBq ¹⁰⁹Cd/rat). Three days later they were injected i.p. with saline or chelating agents (400 μmol/kg) every other day for 2 weeks. At the end of the experiment, the rats were killed and the tissue distribution of cadmium was determined from radioactivity. *a)* The values represent the mean ± S.D. for 5 animals. *b)* Significantly different from control at *p* < 0.05. *c)* Significantly different from BGD at *p* < 0.05. *d)* Significantly different from HBGD at *p* < 0.05.

TABLE V. LD₅₀ Values of Chelating Agents in Mice

Chelating agent	LD ₅₀	
	(mmol/kg)	(mg/kg)
BGD ^{a)}	11.16	4320
HBGD	26.50	10570
CBGD	> 30.0	> 12390
MeOBGD ^{b)}	10.0	3990

Chelating agents were administered i.p. to groups of 6 mice per dose. Survival was recorded at the end of 14 d. *a)* The values were cited from reference 19. *b)* The values were cited from reference 22.

shown in Table IV. BGD, HBGD, and MeOBGD significantly reduced the cadmium deposited in the liver and kidney. The reducing effect of MeOBGD on the hepatic cadmium content was significantly larger than that of BGD or HBGD. The reducing effect of HBGD on the renal cadmium content was significantly larger than that of MeOBGD.

The body weight gain of rats was not significantly affected by the administration of BGD, HBGD, and MeOBGD (data not shown). The LD₅₀ values for BGD, HBGD, CBGD, and MeOBGD are shown in Table V. The LD₅₀ values of HBGD and CBGD were lower than those of BGD and MeOBGD.

In conclusion, the present study reveals the MeOBGD is more effective than BGD, HBGD, and CBGD in removing cadmium from the body. Its effect is mainly due to the great acceleration of fecal cadmium excretion. However, HBGD is more effective than MeOBGD in decreasing the cadmium content in the kidney, the critical organ in cadmium toxicity. Since the acute toxicity of HBGD is much less than that of BGD or MeOBGD, the therapeutic effect of HBGD on cadmium-induced renal damage is suggested to be greater than that of BGD, CBGD, or MeOBGD.

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