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Effect of Cadmium-Mobilizing Dithiocarbamates on Essential Trace Metal Metabolism in Rats

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Dithiocarbamate analogs have been shown as the most effective chelating agents in mobilizing cadmium from rodents (Jones et al., 1988; Gale et al., 1989). High efficacy of these agents has been shown in mice and rats, both in cases of early and late administration after cadmium introduction into the body (Jones et al., 1988; Gale et al., 1989). Beside their high efficacy, in the case of their late application, these agents have advantages over other chelants used for cadmium elimination since they have much lower toxicity (Kojima et al., 1987).

One of the possible explanations for the pathogenesis of toxic chelate effects is based on the interaction between chelating agent and endogenous essential metals. The stability of the calcium chelates is lower by several orders of magnitude than the stability of the chelates formed with endogenous essential trace metals and the toxicity of such chelating agents may be therefore due to the mobilization or binding in situ of certain metals and a consequent impairment of metal-controlled or -activated systems. Thus it has been shown that CaEDTA when given at a normal therapeutic dosage to humans, leads to an increased urinary excretion of Fe, Mn, Cu and particularly Zn (Teisinger and Fišerova-Bergerova, 1958; Truhaut et al., 1966). Repeated administration of toxic doses of CaDTPA resulted in an extensive reduction of the Mn content in liver and small intestine (Nadolny, 1971). The Zn content in skeleton, pancreas, small intestine and testes, show only a slight transient decrease (Auth, 1973) under such conditions. Apparently, the depleted Zn stores are replenished rapidly by Zn absorbed from the

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intestine. Slobodien et al. (1973) observed that when CaDTPA was applied over an extended period of time in humans, each CaDTPA dose resulted in a urinary Zn excretion 20-30 times higher than the pretreatment levels. This indicates that the depletion of Zn stores is transient. 2,3-dimercaptopropane-1-sulfonate (DMPS) and D-penicillamine (PA) significantly increased copper excretion and decreased its concentration in the kidney (Planas-Bohne, 1979).

The purpose of the present study was to evaluate the effect of three chelating agents N-benzyl-N-dithiocarboxy-D-glucamine (BDCG), N-methyl-N-dithiocarboxy-D-glucamine (MDCG) and sodium N-(4-methoxybenzyl)-D-glucamine dithiocarbamate monohydrate (MeOBDCG) which were previously found very effective in reducing cadmium retention and enhancing its elimination from the body on concentrations of some essential elements in the liver and kidney in rats and on their urinary excretion.

MATERIALS AND METHODS

The experiment was performed on 6-week-old albino female rats (about 140 g body weight) from the Institute's breeding farm. They received standard rat diet and tap water ad libitum and were placed in individual metabolic cages for collection of urine. They were divided into four groups according to the chelating agent administration. The first group served as a control and received during 10 days 0.9% saline solution intraperitoneally. The second group received N-benzyl-N-dithiocarboxy-D-glucamine (BDCG), the third group N-methyl-N-dithiocarboxy-D-glucamine (MDCG) and the fourth sodium N-(4-methoxybenzyl)-D-glucamine dithiocarbamate monohydrate (MeOBDCG). Chelating agents were administered intraperitoneally daily for 10 days at a dose of 0.5 mmol/kg body weight/day. 24 hr after the last treatment rats were anaesthetized with ether and exanguinated. Excess moisture from the liver and kidneys was removed by filter paper and the wet weight determined. The right kidney and about 2 g of liver tissue from various parts were wet digested with nitric acid (DS-40, Tecator, Sweden) for trace element analysis by flame atomic absorption spectrophotometry (Pye Unicam SP 9). During the first two and last two days of the experiment, the urine was collected for trace element analysis with the exception of the group which received MDCG. Urine was evaporated and dry ashed at 450 °C. The ash was dissolved in 2 per cent nitric acid adjusted to 10 ml and iron, zinc, copper and calcium were measured by flame atomic absorption spectrophotometry. For statistical treatment of data Student's t-test was used (significance level $P<0.01$).

Table 1. Concentration of iron, zinc and copper in the liver and kidney (μg/g wet tissue)

			Fe	Zn	Cu
LIVER	20[c]	C[a]	176.4± 7.9[b]	40.0±0.9	8.1±0.8
	20	E_1	189.7± 6.7	40.4±1.1	8.9±0.7
	10	E_2	178.0± 8.0	42.1±0.9	6.1±0.4
	10	E_3	202.5±14.6	36.9±1.1	10.4±1.2
KIDNEY	20	C	52.7±1.6	30.2±0.6	12.6±0.7[d]
	10	E_1	56.0±4.4	30.2±1.1	9.1±0.7[e]
	10	E_2	62.0±3.2	29.9±0.6	9.6±0.4
	10	E_3	53.7±1.6	31.1±0.7	15.3±1.2

[a]C - control group received i.p. 0.9% saline

Chelating agents BDCG (E_1), MDCG (E_2), MeOBDCG (E_3) were administered intraperitoneally at a dose of 0.5 mmol/kg body weight during 10 days.

[b]Arithmetic mean ± SEM

[c]Number of animals in the group

[d]$P<0.01$ compared to controls

[e]$P<0.001$ compared to controls

Table 2. Excretion of iron, zinc, copper and calcium in urine (μg/48 hr)

		Fe	Zn	Cu	Ca
CONTROL	I	18.4±2.1[b]	36.1±3.0	11.4±1.3	6.3±1.3
	II	22.8±5.2	49.2±3.7	19.7±2.5	9.6±0.6
E_1-BDCG[a]	I	16.8±2.5	35.7±2.5	10.0±1.3	10.0±1.0
	II	14.0±2.2	41.3 ±2.7	11.3±1.1[c]	11.3±0.9
E_3-MeOBDCG	I	18.0±3.0	38.6±4.2	21.9±3.9	9.3±1.4
	II	29.4±7.0	47.6±3.1	26.3±5.4	11.2±0.5

[a]Chelating agents BDCG (E_1) and MeOBDCG (E_3) were administered i.p. at a dose of 0.5 mmol/kg body weight during 10 days.

[b]Arithmetic mean ± SEM of 10 animals in each group.

Urine was collected during first (I) and last (II) 2 days (48 hr) of the experiment

[c]$P<0.01$ compared to controls

RESULTS AND DISCUSSION

During the experimental period of 10 days the weight gain was similar in all three groups (about 13 g - 8%). The concentrations of analyzed trace elements in the liver and the kidney were in most groups, similar to the control values (Table 1). Only the concentration of Cu in the kidney after BDCG and MDCG treatment was lower than in the control group. The administration of BDCG or MeOBDCG did not increase the excretion of trace elements in urine (BDCG even decreased Cu elimination) (Table 2). The results obtained indicate that in our experimental conditions chelation therapy did not increase essential element excretion from the body. This is different from the results obtained previously with other chelating agents. With the exception of modest reductions in the copper levels of the kidneys for BDCG and MDCG, the iron, zinc and copper levels of the liver and the kidneys were not significantly different from those of the controls. The urinary excretion of iron, zinc, copper and calcium were also not significantly higher from those of the controls. It should be mentioned that changes in trace element content after CaEDTA or CaDTPA treatment were usually observed with single administration of high doses (2-4 mmol/kg body weight; Nadonly, 1971; Auth, 1973). The dose used in our experiment was lower (0.5 mmol/kg b. w.) but given during 10 days. The results obtained are interesting since until now this aspect of dithiocarbamate treatment was not investigated. High efficacy and low toxicity of these dithiocarbamate analogs indicate their possible applicability in cases of chronic cadmium intoxication.

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