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Effect of Short-Term Ethanol Administration on Cadmium Excretion in Rats

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In modern toxicology great attention has been paid to the problem of interactions between xenobiotics occurring in the organism. It results from simultaneous exposure to two or more toxic substances, which very often takes place under occupational and/or environmental conditions.

Interactions between cadmium (Cd) and ethanol (Et) are an important problem in the field of modern toxicology. Both substances induce a risk to human and animal health (Schioeler 1991; WHO 1992). Exposure to Cd can occur in the workplace and in the environment because this metal is utilized in a number of industrial practices and is a ubiquitous contaminant of the natural environment and dietary products (WHO 1992). The excessive consumption of Et in the form of alcoholic beverages by part of the population exposed occupationally and/or environmentally to Cd is a common problem in almost all industrialized and developing countries (Schioeler 1991). In the available literature no data on Cd levels in alcoholics as compared to non-alcoholics has been found. Wójcik and Brzeski (1997) studied blood Cd concentration of patients with acute Et intoxication and patients chronically dependent on Et. These authors have noted that Cd levels in these persons were low and belonged to the lower range of hygienic standards. As they had not a control group any conclusion about Et influence on Cd concentration is impossible.

Taking the above into consideration some authors have studied the interactions between Cd and Et in experimental animals (Tandon and Tewari 1987; Hopf et al. 1990; Sharma et al. 1991, 1992; Gałażyn-Sidorczuk et al. 1998). Previously we reported (Gałażyn-Sidorczuk et al. 1997) that Et administered in the last phase of Cd oral exposure led to its increased concentration in the rat tissues. In this regard, our data are in accordance with the results of other authors (Tandon and Tewari 1987; Sharma et al. 1991, 1992). According to our hypothesis Et-induced increase in Cd body burden (Tandon and Tewari 1987; Sharma et al. 1991, 1992; Gałażyn-Sidorczuk et al. 1997) can result from its influence on Cd gastrointestinal absorption and/or urinary excretion. Based on this suggestion Cd excretion in urine and feces was assessed by us and results are presented in this paper.

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MATERIALS AND METHODS

The experiment was conducted on 24 male Wistar rats of initial body weight of 180-200 g. The animals were divided into the following four experimental groups of 6 animals each: received redistilled water to drink during the whole course (8 weeks) of the experiment (control group), received by a stomach tube, 25% water solution of Et in the dose of 0.625 g/kg (converting to absolute alcohol), every 12 hr for the last 108 hr of the experiment (Et group), exposed to a water solution of cadmium chloride ($CdCl_2$) at the concentration of 50 mg Cd/L for 8 weeks (Cd group) and received 50 mg Cd/L of drinking water for 8 weeks and Et (0.625 g/kg p.o.) every 12 hr for the last 108 hr of the intoxication with Cd (Cd + Et group).
At the same time when the rats from the Et and Cd + Et groups received Et those from the control and Cd group were administered redistilled water by a stomach tube.
Throughout the whole experiment the animals had an unlimited access to the LSM granulated diet and drinking water (calibrated bottles) (control and Et groups - redistilled water; Cd and Cd + Et groups - water solution of $CdCl_2$). The 24-hr consumption of drinking water during the whole course of the experiment was assessed.
Twenty four hr before the end of the exposure the animals were placed in glass metabolic cages for 24-hr collection of urine and feces when they had access to drinking water only.
The concentration of Cd in the 24-hr samples of urine and feces was determined by the atomic absorption spectrometry method (AAS) with the use of electrothermic atomization. The recovery of the method for Cd was 97.2%.
The results elaborated statistically using the ANOVA test are presented in tables as arithmetical means, standard deviation and statistical significance (p) for 6 rats in each group. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The present work was aimed at studying the influence of short-term Et administration on urinary and fecal Cd excretion in rats continuously exposed to this metal in drinking water.

The level of Cd exposure used in this study (50 mg/L) corresponds to human, especially smokers, exposure to this metal under occupational conditions or in heavy contaminated areas. Et was administered to rats in the dose (0.625 g/kg every 12 h for 108 h) which can correspond to consumption of less than 100 g of 45 % vodka in man.

Mean intake of Cd with drinking water in the groups of rats is presented in Table 1. Et administered intragastrically in the final phase of Cd exposure had no influence on Cd consumption.

Table 1. Cd intake with drinking water

Group	Mean consumption of drinking water (ml/24h/rat)	Mean Cd consumption (μg Cd/24h/rat)	Total Cd consumption (mg Cd/rat)
Control	37.5 ± 1.7	———	———
Et	37.0 ± 2.0	———	———
Cd	27.5 ± 1.3[a]	1375.0 ± 65.0	77.00 ± 3.64
Cd + Et	27.4 ± 1.9[a]	1370.0 ± 95.0	76.72 ± 5.32

Mean ± SD of 6 animals

[a] statistically significant versus the control group ($p < 0.001$)

Control group – redistilled water to drink; Et group – received ethanol alone; Cd group – was exposed to cadmium; Cd + Et group – received cadmium and ethanol. For details see Materials and Methods

As can be seen from Table 2, the rats unexposed to Cd (control animals and those given Et alone) had very low and negligible fecal excretion of this toxic element as compared to rats of the Cd – group and rats of the Cd + Et group. Cd concentration in the LSM granulated diet was vestigial thus Cd intake with the diet was also negligible compared to its intake with drinking water in the exposed animals and had no influence on the results. In rats intoxicated with Cd its concentration in the 24-hour collection of feces was very high when compared to the 24-hour total Cd oral intake. It is in accordance with the findings of other investigators (Piotrowski et al. 1986; Weigel et al. 1987) who found that only small portion of consumed metal was absorbed by rats.

In humans and in experimental animals Cd gastrointestinal absorption is very low and in rats it amounts only about 2% of the metal ingested daily (Piotrowski et al. 1986; Weigel et al. 1987). Absorbed Cd is excreted via urine, bile and desquamated intestinal mucosa while the unabsorbed part of ingested metal is eliminated from the body in feces. The quantity of the endogenous element excreted via gastrointestinal tract is very low in comparison to the unabsorbed portion. A large proportion of the fecal Cd, directly related to the daily oral intake of this metal, reflects mainly the unabsorbed part of ingested Cd. Thus the fecal Cd is a good and a very useful indicator of the daily Cd intake via food and water (Lauwerys et al. 1994).

Et administered intragastrically in the final stage of the Cd exposure led to a statistically significant decrease in the fecal excretion of this trace element in comparison with its excretion in animals which received Cd alone (Table 2). On the

Table 2. Urinary and fecal Cd excretion

Group	Urine (μg/24h/rat)	Feces (μg/24h/rat)
Control	0.206 ± 0.034	1.48 ± 0.35
Et	0.198 ± 0.037	1.53 ± 0.28
Cd	2.712 ± 0.34[a]	1239.86 ± 80.13[a]
Cd + Et	1.995 ± 0.241[a b]	1020.73 ± 76.65[a b]

Mean ± SD of 6 animals
[a] statistically significant versus the control group ($p < 0.001$)
[b] statistically significant versus the Cd group ($p < 0.001$)
Legends the same as for Table 1

basis of Cd intake with drinking water and its fecal excretion we have found that the rats exposed to Cd alone excreted from the gastriontestinal tract 90.2 ± 4.3% of the consumed metal, while those co-exposed to Cd and Et excreted significantly ($p<0.001$) less of this metal (74.5 ± 5.8%). Taking into consideration the fact that oral Cd intake in animals which received Cd alone and those co-exposed to this metal and Et (Table 1) was at the same level, the Et-induced decrease in the fecal Cd excretion could indicate that the alcohol increased Cd gastrointestinal absorption. It is known that Et increases the permeability of biological membranes making them more permeable to various substances, including metals (Gulati et al. 1985). Based on this supposition one can accept that Et also increases Cd absorption from the gastrointestinal tract and its uptake and accumulation in various tissues and organs (Sharma et al. 1991, 1992; Gałażyn-Sidorczuk et al. 1997).

Cd is characterized by a very strong ability to accumulate in the organism, especially in the kidney and liver in the form connected with metallothionein. The amount of Cd body burden, particularly its concentration in the kidney can be assessed on the basis of its urinary excretion (Lauwerys et al. 1994).
At low and moderate exposure the urinary Cd mainly reflects Cd body burden, particularly the amount accumulated in the kidney. Under these conditions the urinary excretion of Cd increases with time of exposure and is correlated clearly with the level in the kidney. When all sites of Cd binding in the body become saturated after excessive or long-term intoxication and the exposure is continued the metal that is still absorbed cannot be further retained and is rapidly eliminated with urine. Thus the urinary Cd excretion is a good indicator of the body burden, as long as renal damage develops (Foulkes 1986; WHO 1992; Lauwerys et al. 1994).

Table 3. Cd concentration in the liver and kidney (for more data on Et influence on Cd concentrations in other tissues see Gałażyn-Sidorczuk et al. 1997)

Group	Liver (μg/24h/rat)	Kidney (μg/24h/rat)
Control	0.029 ± 0.008	0.064 ± 0.010
Et	0.067 ± 0.020	0.086 ± 0.013
Cd	8.880 ± 1.395[a]	17.354 ± 0.707[a]
Cd + Et	13.586 ± 1.581[a b]	18.806 ± 1.049[a c]

Mean ± SD of 6 animals
[a] statistically significant versus the control group ($p < 0.001$)
[bc] statistically significant versus the Cd group ($p < 0.005$ and $p < 0.05$, respectively)
Legends the same as for Table 1

In the control animals and those treated with Et alone, the urinary excretion of cadmium was low in comparison to its excretion in rats exposed to Cd and co-exposed to Cd and Et (Table 2). Et given alone had no effect on Cd excretion, but administered to the animals intoxicated with this metal led to a statistically significant decrease in its urinary excretion.

The Et-induced increase in the intestinal Cd absorption (Gałażyn-Sidorczuk et al. 1997) is a cause of an increase in Cd concentrations in various tissues, especially in the liver and kidney – the main organs of its accumulation (Table 3). This increase is connected with an ability of Et to induce metallothionein synthesis (Gałażyn-Sidorczuk et al. 1998). Elevated Cd retention in the body may in consequence lead to reduction in urinary Cd excretion as it has been noted in this study in rats exposed simultaneously to these substances.

Results of this paper, in conjunction with our previous study (Gałażyn-Sidorczuk et al. 1997, 1998), suggest that under conditions of co-exposure to Cd and Et the urinary Cd excretion probably can not be a useful indicator of this metal body burden. As we reported previously (Gałażyn-Sidorczuk et al. 1997) Et increased accumulation of the metal in the kidney and at the same time decreased its urinary excretion (in this study). The Et-induced increase in Cd accumulation in the kidney was not accompanied by a simultaneous increase in urinary Cd.
In the available literature there are some data on the interactions between Et and Cd (Tandon and Tewari 1987; Hopf et al. 1990; Kershaw et al. 1990; Sharma et al.

1991, 1992) but we have found no data on the influence of Et on Cd excretion. This makes wider discussion of our results rather difficult.

The present investigation has shown that Et, consumed under conditions of exposure to Cd, leads to the decrease in fecal and urinary Cd excretion. These changes result from the Et-induced increase in Cd absorption and retention. The Et-induced enhanced Cd absorption and retention in the body lead in consequence to an increase in Cd accumulation in various tissues as was described previously by us (Gałażyn-Sidorczuk et al. 1997).
Et increasing Cd absorption and body burden (Tandon and Tewari 1987; Sharma et al. 1991, 1992; Gałażyn-Sidorczuk et al. 1997, 1998) makes the organism more vulnerable to its toxic action.
Because often long-term Et consumption takes place and taking into consideration the fact that even short-term Et administration can modify Cd metabolism we are planning studies on interactions between these xenobiotics under conditions of chronic Et exposure.

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