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Effect of Nickel (II) Chloride Oral Exposure on Urinary Nickel Excretion and Some Other Elements

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Abstract

Male Wistar rats were given nickel (II) chloride ($NiCl_2 \cdot 6\ H_2O$) with drinking water (300 or 1200 ppm Ni for 90 days). Urine volume and nickel, zinc, copper, calcium and inorganic phosphorus were measured in 24 h urine after 45 and 90 days of exposure. The results demonstrate that relatively low–level oral exposure (300 ppm Ni) induces an increase of urinary Ni excretion ($p < 0.001$), but no significant changes in other elements. The higher Ni dose (1200 ppm) caused elevation of this metal in urine ($p < 0.001$), as well as significant changes of urinary volume, and zinc, copper and inorganic phosphorus concentration.

Keywords: urinary excretion, nickel, zinc, copper, calcium, inorganic phosphorus

Introduction

Drinking water and food are the main sources of nickel exposure for the general population [1,2].

Following oral administration of nickel compounds to experimental animals, even at very high doses, this metal is absorbed poorly from the gastrointestinal tract [1,3]. However, in human volunteers the mass fraction of nickel absorbed from water averaged 40-times the corresponding value absorbed from food [4].

In general, relatively low gastrointestinal absorption explains the elimination of dietary nickel in faeces. In human beings and animals urinary excretion is usually the major clearance route for absorbed nickel [1].

Based on the literature survey, it can be noticed that there are few reports on the urinary elimination of this metal taken orally [5-8].

According to some authors nickel may alter the metabolism of several essential metals, e.g. by affecting normal tissue distribution of zinc, copper, chromium, manganese, iron after parenteral or dietary administration [8-12].

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The present investigation was undertaken to detect the urinary Ni excretion and to evaluate the level of some other elements in the urine of rats after administration of nickel (II) chloride in drinking water.

Experimental Procedures

The experimental animals (42) were male rats of the Wistar strain with an average initial body weight of 210 ± 23 g. The rats were divided into three groups of 14 rats each.

Control group (C) received tap water to drink, whereas the animals of the two exposed groups received the water solution of nickel (II) chloride ($NiCl_2 \cdot 6\ H_2O$) at the concentration of 300 (Ni-300) and 1200 ppm Ni (Ni-1200), respectively, for 90 days.

The rats had unlimited access to the standard diet (food pellets, Labofeed B, PN-ISO 9001, Poland) and tap water or water solution of $NiCl_2$. After 45 and 90 days of exposure the control and exposed animals of each group were placed in individual metabolic cages (Simax, Czech Republic) to collect 24 h urine (no food was given during urine collection). Next, the urine volume was measured

Table 1 . Effect of exposure to Ni(II)Cl_2 in drinking water on the urinary volume and excretion of nickel, and some other elements.

Parameter	Group	Time - days	
		45	90
Urinary Volume cm^3/24h	C	14.7 ± 4.3	11.9 ± 7.3
	Ni-300	16.6 ± 13.5	13.7 ± 5.6
	Ni-1200	21.9 ± 12.3	27.3 ± 11.0*
Nickel µg/24h	C	0.33 ± 0.16	0.23 ± 0.07
	Ni-300	29.2 ± 11.8***	29.1 ± 9.5***
	Ni-1200	221.7 ± 95.2***	215.7 ± 126.6**
Zinc µg/24h	C	5.5 ± 1.7	5.2 ± 0.9
	Ni-300	4.8 ± 1.6	5.0 ± 0.9
	Ni-1200	5.2 ± 1.7	8.6 ± 2.1**
Copper µg/24h	C	2.28 ± 0.95	2.00 ± 0.31
	Ni-300	2.44 ± 1.69	2.35 ± 0.62
	Ni-1200	0.66 ± 0.19**	0.83 ± 0.53*
Calcium µg/24h	C	0.69 ± 0.38	0.59 ± 0.33
	Ni-300	0.81 ± 0.51	0.70 ± 0.46
	Ni-1200	0.87 ± 0.65	0.78 ± 0.48
Inorganic phophorus mg/24h	C	10.1 ± 3.3	10.5 ± 2.8
	Ni-300	8.2 ± 2.5	11.5 ± 2.6
	Ni-1200	7.4 ± 2.7	6.3 ± 2.1*

*p< 0.05; **p< 0.01; *** p< 0.001, significantly different from control values

and the samples were centrifuged (WE – 6 centrifuge, 3000 rev/min., 10 min).

Measurements of calcium and inorganic phosphorus were immediately performed using Dimension clinical chemistry system (reagents of DADE BEHRING).

For nickel, zinc and copper determination, the urine samples were acidified with concentrated nitric acid (Ni), or chloric acid (Zn and Cu) [13,14]. Until analysis, the urine specimens were stored in closed plastic tubes at -20°C.

Nickel in the urine was measured by electrothermal atomic absorption spectrophotometry (Varian Spectr AA. 250 Plus) using the graphite furnace technique [13]. The detection limit for nickel determination by this technique was 0.7 ng/cm^3.

Zinc and copper contents were analyzed by flame atomic absorption spectrophotometry (Varian Spectr AA. 250 Plus).

The accuracy of the determination of metals (Ni, Zn, Cu) was tested with Reference Material Seronorm Trace Elements Urine (Nycomed, Norway). The metal concentrations measured in these materials were in good agreement with the recommended values given by the producer.

The results were expressed per 24 h and evaluated statistically using the Student's t-test. A comparison was made between control group and the two nickel-treated groups. Data in Table 1 represent arithmetical mean ± standard deviation (SD), as well as statistical significances (p) for 5-7 rats.

Results and Discussion

During the measurement of the excretion of total urine as one of the basic tests it can be noticed in the treated rats, particularly in the 1200 ppm Ni group that there is a considerable individual variation of urine volume (Table 1).

After a detailed analysis of the results there were not any significant differences between control and 300 ppm Ni exposed rats. These measurements agree well with our previous findings for 200 ppm Ni [15]; however, conversely Clary [16] observed significantly reduced urine volume in the rats receiving drinking water containing 225 ppm Ni (as $NiCl_2$). According to the author the decreased urine output may be due to decreased water consumption and also to the action of nickel, which is reported to have an antidiuretic effect.

In our experiment, after the higher nickel dose (1200 ppm) the rats excreted more total urine than the controls, which is regarded as a pathological phenomenon (at 45

d. increase of 50% above control, and at 90 d. - 130%, $p < 0.05$). This might indicate tubular dysfunction causing impaired urine condensation [17]. This is more probable since the animals in this group drank less 1200 ppm Ni solution in comparison both to Ni-300 ppm group, and control group, in accordance with the results in our previous publication [18].

Measurements of nickel concentrations in urine and serum provide laboratory indices of occupational and environmental exposures to nickel compounds [19]. During this experiment urinary excretion of nickel by control rats varied between 0.33 ± 0.16 at 45 d., and 0.23 ± 0.07 μg/24 h at 90 d., respectively (see Table 1).

As expected, after oral administration of nickel (II) chloride, the levels of metal in the urine of all exposed rats were significantly higher than in those of the controls.

The excretion of Ni in rats of the 300 ppm treated group was 29.2 ± 11.8 μg/24 h at 45 d., in the 1200 ppm Ni group – 221.7 ± 95.2 μg/24 h ($p < 0.001$).

These values were not significantly changed up to 90 d. of exposure. Therefore, Ni excretion in urine did not show any tendency to increase with ingestion time. Also Severa et al. [7] found no significant differences between nickel concentration in the urine of rats exposed to nickel sulphate (100 ppm Ni in drinking water) for 3 months and of those exposed for 6 months.

We concluded that Ni excretion in urine was closely associated with nickel intake and this is in agreement with the findings of Oosting et al. [8].

In general, throughout the exposure time nickel concentration in the urine of the 1200 ppm Ni group was about 7.5 times higher than that in the 300 ppm Ni group (see Table 1).

Regarding the mean daily consumption of nickel per rat of the two exposed groups [18] with metal levels in the urine, the elimination rate of Ni was only a small percent of daily intake dose (0.35 % for the 300 ppm, and 0.80 % for the 1200 ppm Ni group).

In our earlier study urinary excretion after exposure to 200 ppm Ni in drinking water was 0.20 % and 0.24 % of the administered dose after 45 d. and 90 d., respectively [15]. In a long term feeding study by Severa et al. [7] rats were given drinking water containing 100 ppm Ni, as $NiSO_4$ for 6 months and the urinary elimination was 2% of the absorbed dose. When mice were given 0.58 mg/kg body weight of $^{63}Ni^{2+}$ (as $NiCl_2$) orally by gastric intubation, the total urinary excretion of Ni in three days was 1.8% of the dose [6]. On the other hand, Ishimatsu et al. [5] found that after a single oral administration to rats of 10 mg Ni (as $NiCl_2$) the level of metal in the urine was 914 μg/24 h (9.14%).

The results of our studies are confirmed by reports of other authors indicating that relatively small amounts of Ni given in drinking water or food are excreted in urine, despite the high accumulation of metal in the kidney [5, 6, 8].

Among the specialised tests in the laboratory diagnostics of kidney diseases is an analysis of the metabolism of essential metals, although in this field nothing has currently been established [17,20]. The present study showed that 90 days oral exposure on 300 ppm Ni did not change the excretion of zinc and copper. On the other hand, 1200 ppm treatment induced significant changes in the levels of these metals. At the termination of the study (90 d.) significantly more zinc was excreted in the urine (65% above controls, $p < 0.01$), while significant diminution in the elimination of copper was observed already at day 45-70% ($p < 0.01$), and next on day 90-60% ($p < 0.05$).

There are only a few reports on the deposition and excretion of these metals after parenterally as well as orally taken nickel compounds. We previously found that in rats exposed to 200 ppm Ni solution for 3 months, the excretion of zinc and copper was within the normal observed limits of control rats [15], whereas Clary [16] found a decreased (65 % below controls, $p < 0.05$) urinary level of Zn induced by the administration of 225 ppm Ni (as $NiCl_2$) in drinking water for 4 months. Oosting, et al. [8] reported that the addition of nickel (II) chloride to the diet up to a concentration of 100 ppm Ni (28 days) had no significant effect on Cu elimination.

In some kidney injuries, and also in other diseases with symptoms of changes in the kidneys' excretion of metabolites, valuable information is supplied by, among other things, daily testing of urinary excretion of calcium and inorganic phosphorus [17,20].

The results of our study demonstrate that the excretion of calcium was influenced only marginally in rats exposed to nickel (II) chloride (300 and 1200 ppm Ni) (see Table 1).

Nickel addition to the drinking water (300 ppm) had no significant effect on inorganic phosphorus. Differences between control and exposed rats were found at the higher exposure (1200 ppm), namely a reduction in the urinary excretion of inorganic phosphorus. The first estimation (at 45 d.) showed an apparent decrease of 27% (not statistically significant), the second (at 90 d.) - 40% ($p < 0.05$), below controls, respectively.

Literature data concerning both calcium and inorganic phosphorus excretion upon nickel salts administration are relatively sparse.

In contrast to our results, Clary [16] found that Ni-exposed rats (225 ppm Ni in drinking water) excreted less urinary Ca than the controls (37%, $p < 0.05$). In the study by Gitlitz [21] i.p. injection of $NiCl_2$ to rats (4 mg Ni/kg) caused a significant decrease ($p < 0.001$) in the urinary level of calcium, without any change in the inorganic phosphorus concentration.

According to the literature, lower inorganic phosphorus urine excretion is observed in, among other things, the early phase of renal lesions, whereas only in the advanced disease stage do there appear disorders in the metabolism of calcium and phosphorus [17,20].

In summary, our studies have shown that among the research carried out the only change occuring in the urine of rats drinking 90 days water containing 300 ppm Ni (as $NiCl_2 \cdot 6\ H_2O$) concerns the significant increase in the

excretion of nickel ($p < 0.001$). As specified in Table 1, the higher Ni concentration in water (1200 ppm) caused moreover changes in urinary volume (increase), as well as changes in the concentration of zinc (increase), copper and inorganic phosphorus (decrease), which was particularly visible after the longer exposure time.

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