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The Effect of Mercury in Iron Metabolism in Rats

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Abstract

Chelation therapy has a long history of use in clinical toxicology to remove heavy metal toxicity from the body. The present research aimed to investigate the potential efficiency of Deferasirox and Deferiprone in removing mercury after its administration for 60 days following two dose levels of 40 mg Hg^{2+}/kg body weight (Low dose drinking of mercury) and 80 mg Hg^{2+}/kg body weight (High dose drinking of mercury) to male Wistar rats every day. After mercury administration some abnormal clinical signs observed in animals. Also after acute exposure of rats to mercury, decreased plasma concentration of iron, therefore it can be cause iron deficiency anemia. Our results showed that the effect of mercury on hematological indices was statistically significant and confirmed the iron deficiency anemia in rats. Combination therapy with Deferasirox and Deferiprone cause that the mercury level present in blood serum was significantly reduced and simultaneously, iron concentrations returned to the normal level and the symptoms of toxicity also were reduced. Also iron deficiency anemia that caused by mercury administration obviated.

Keywords: Mercury toxicity; Combination therapy; Iron deficiency anemia; Rats

Introduction

Metals such as iron, Zinc, and copper (essential elements) that present on living organisms are critical to them, whereas metals such as lead, cadmium, and arsenic that they are also present on living organisms have no known biologic role. Some other metals such as thallium and mercury which are naturally not present on living organisms are toxic elements and cause serious damages for them by interaction with essential elements.

Mercury (Hg) is known to be one of the most toxic heavy metals and it can markedly alter the metabolism and function of such essential trace elements as copper, zinc, iron, manganese, selenium and calcium by competing for ligands in biological systems [1]. Hg is considered toxic to the kidneys, central nervous system, cardiovascular, gastrointestinal, and immune systems [2,3]. Acute toxic effects are generally anticipated at levels of 50 µg Hg/L blood, compared with normal (no effect) levels of up to 10 µg Hg/L blood in humans [2]. In our previous experiments on rats we investigate the chelation potency of Deferasirox given to animals after cadmium and thallium loading. Our results showed that cadmium and thallium concentrations increase in blood serum after their administration while the iron level decreases, therefore it can cause iron deficiency anemia [4,5]. Anemia is a pathologic process in which the hemoglobin (Hb) concentration in red blood cells is abnormally low. There is no doubt that iron (Fe) deficiency is the cause of most forms of anemia. Iron-deficiency anemia is characterized by the reduction or absence of Fe stores, low serum concentrations of Fe and Hb, decreased hematocrit, an increased platelet count [6], low rate of Transferrin Saturation (TS), low serum ferritin, and a marked increase in Total Iron-Binding Capacity (TIBC).

The specific role of Transferrin (TF) as the iron-transport protein of mammalian serum and its iron-binding properties are well known. Under physiologic conditions only one third of the TIBC of TF is saturated with Fe, i.e. the predominant fraction is presented as the Fe-free Apo Transferrin (ATF) [7]. Serum Iron (SI) and the Total Iron-Binding Capacity (TIBC) are often used to determine the need for hospital admission and chelation therapy after an iron overdose.

In medicine, chelation therapy is gaining increased acceptance in order to balance concentrations of essential metal ions in the body and to remove undesirable metal ions [4,5,8-11]. Recently in chelation therapy, many candidate compounds have been screened in animal models [11]. In our laboratory, we have been investigating the effects of two alternative orally effective chelating drugs, Deferasirox (DFX) and Deferiprone (DFP: L1), as combined in removing mercury from the body in vivo using animal models.

The synthesis of deferasirox (4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic acid, DFX or ICL670, Figure 1) was first reported in 1999 [12]. It is a tridentate chelator and shows little affinity for divalent ions such as Zn^{2+} or Cu^{2+} [13]. In vivo, this selectivity is demonstrated by conserved plasma Zn and Cu levels in patients taking deferasirox, and while its efficacy is rather low for inducing negative iron balance, it is effective and well-tolerated [14,15]. Deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one, DFP or L1, Figure 1), which belongs to the family of α-ketohydroxpyridines, can remove excess iron from various parts of the body of iron-loaded patients, including the liver and, particularly, the heart [16]. The drug is also used worldwide

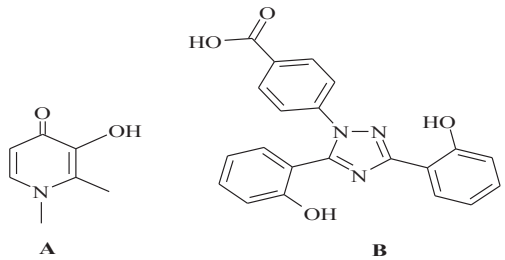

Figure 1: Chemical structures of deferiprone (A) and deferasirox (B).

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to treat cancer, leukemia, and other diseases. It is worth noting that the drug deferiprone may be used in the detoxification of other metals, such as aluminum in hemodialysis patients, plutonium in nuclear industry workers, and uranium in some military personnel [17-19].

The aim of the present study was to show that mercury could affect on iron metabolism. Since the iron is one of the essential trace elements which have crucial metabolic and hematologic effects, therefore decreasing of iron in the presence of mercury lead to iron deficiency anemia. Also we propose chelation therapy for removing iron deficiency anemia that caused by mercury administration.

Materials and Methods

Maintenance of the animals

Male growing Wistar rats with initial mean body weight of 200g were housed individually in plastic cages with glassgridded bottoms and maintained under controlled temperature (23 ± 1°C), humidity (55%) and light/dark cycle (12/12 hours). Experiments were performed on seven-week-old male Wistar rats. They are bred in animal house at Mashhad University of medical science, Mashhad, Iran. This study was approved by the ethics committee of Ferdowsi University of Mashhad, Mashhad, Iran and Mashhad University of medical science, Mashhad, Iran.

Apparatus

Atomic absorption spectrometer (F AAS and GF AAS) Model Varian was used for measurement of mercury and iron concentrations in rats' blood, respectively.

Materials

Deferasirox and deferiprone were purchased from Novartis Co. (Basel, Switzerland). Mercury (II) chloride was purchased from Merck.

Experimental design

During 3 days of adaptation to new surroundings rats were given a cereal-based stock diet and then they were divided into 3 groups. Consequently after acclimatization of animals, we assigned them randomly to control and treated groups. The first group containing 10 rats (control group) was given normal food and distilled water to drink. The second and third groups were given water containing mercury to the extent of 40 mg Hg^{2+}/kg body weight (low dose drinking of mercury) and 80 mg Hg^{2+}/kg body weight (high dose drinking of mercury), respectively. The second and third groups consisted of 30 animals in each group. Oral administration of toxic metal ion was performed once a day. The consumed dosing volume for animals was calculated based upon their weight. During this time since mercury administration, its toxicity symptoms gradually were appeared. After 60 days, the animals in each group (except control group) were divided into three sub-groups containing 10 rats; before chelation therapy group (control), without chelation therapy group and combination therapy with deferasirox and deferiprone. Chelation therapy period started immediately after mercury administration within 10 days. Mercury toxicity symptoms observed in rats have been removed in a short term after drug administration. Classification of animals is shown in Table 1.

After 60 days, the first group of rats were anesthetized with ether vapors and immobilized by cervical dislocation. Animals were sacrificed by exsanguinations from abdominal aorta; and blood samples were collected for determination of iron and mercury concentrations by graphite furnace atomic absorption spectroscopy (GF AAS). After 10 days of the chelation therapy period, the second and third groups of rats were killed by exasanguination from the abdominal aorta and blood collected for determination of the mentioned parameters [20]. Also at the end of this step, some hematological indices such as Hemoglobin (Hb) concentration in red blood cells, serum iron concentration, Total Iron Binding Capacity (TIBC), serum mercury concentration and etc. were determined [4,5].

	Classification of animals during period of mercury administration		Classification of animals after mercury administration (chelation therapy period)
All rats	**Control group**		
	drinking group	**High dose drinking of mercury** (80 mg Hg^{2+}/kg body weight)	**Before chelation therapy**
			Without chelation therapy
			Combination therapy with DFX (70 mg/kg body weight) + **DFP** (150 mg/kg body weight)
		Low dose drinking of mercury (40 mg Hg^{2+}/kg body weight)	**Before chelation therapy**
			Without chelation therapy
			Combination therapy with DFX (70 mg/kg body weight) + **DFP** (150 mg/kg body weight)

Table 1: Classification of animals.

Group	Control	Low dose drinking of mercury	High dose drinking of mercury
Initial body weight[a] (g)	205 ± 7(10) (day 1)	200 ± 4(30) (day 1)	195 ± 3(30) (day 1)
Final body weight[a] (g)	275 ± 7(10) (day 60)	245 ± 8(29) (day 70)	215 ± 7(28) (day 70)

[a] Main of five determination ± standard deviation

(Values in parentheses are the number of animals in each group)

Table 2: Body weights over 60 days for rats in different groups.

Statistical analysis

Determination of mercury and iron in samples was carried out by atomic absorption spectrometry by standard addition method. The values are expressed as mean values (at least three separate determinations) Standard Error of the Mean (SEM). The data were subjected to statistical analysis by Student's t-test; $p<0.05$ was considered significant.

Result

Mercury toxicity symptoms observed in rats in a short term after mercury administration. Some of mercury toxicity symptoms appeared during a period of mercury uptake was appearance of red staining around the eyes, hypotonia (muscle weakness), increased sensitivity to light, and loss of hair and weight. There were slight differences between the groups in the initial body weight of the rats (mean 200g), but at the end of mercury administration experiment, those rats which mercury has been added to their diets, had significant weight loss (Table 2). Comparison of the weights in this experiment shows dietary treatment affected the food intake, whereby animals given a normal diet consumed more food than those given mercury. Also because of the slight (but significant) differences in body weight of rats at the start of the study, the results can be influenced by the initial classification and assignment of rats to treated groups. Therefore the Day 1 group body weights are notable and they must be considered. Also it must be mentioned that after acclimatization of animals, we assigned them randomly to control and treated groups. Also Histopathological findings of mercury-poised rats are valuable and precious data that can confirm the effect of mercury toxicity in rats' (and other biological models) tissues [21-23] (Table 2).

Hematological indices	Control	Low dose drinking of mercury	High dose drinking of mercury
Serum iron (µg/dL)	138.65 ± 12.623	92.256 ± 7.195	68.325 ± 6.233
TIBC (µg/dL)	284.34 ± 23.18	1667.4 ± 21.72	1789.8 ± 324.2
TS (%)	47.521 ± 7.192	5.91 ± 0.53	3.70 ± 0.25
Serum ferritin (µg/L)	82.523 ± 2.711	54.105 ± 1.214	50.250 ± 1.253
Hemoglobin (g/dL)	14.790 ± 1.898	9.988 ± 1.334	8.025 ± 1.961
Platelet (10^9/L)	738.10 ± 52.21	1370.13 ± 82.90	1362.25 ± 74.25
RBCs (10^{12}/L)	7.100 ± 0.973	6.838 ± 0.973	6.864 ± 1.436
HCT (%)	40.810 ± 5.097	28.763 ± 1.894	27.010 ± 1.636
MCV (fL)	58.20 ± 1.21	42.108 ± 3.147	39.351 ± 1.369
MCH (pg)	20.980 ± 0.859	14.352 ± 1.864	11.592 ± 0.342
MCHC (g/dL)	36.250 ± 1.159	35.015 ± 2.229	30.700 ± 1.124

Table 3: Hematological indices in various groups of rats after mercury administration (Results are present as arithmetic means ± SEM, Significant at $p<0.05$ when compared with control).

Impacts of mercury on hematological indices in rats

Chelation therapy period started immediately after mercury administration during two weeks. Mercury toxicity symptoms observed in rats have been removed in a short term after drug administration.

The effect of mercury on hematological indices was statistically significant. During mercury administration, its concentration increased in blood serum while iron level decreased. Furthermore, our results showed that mercury accumulations in blood at higher dose levels were more than the lower dose levels. After the chelation therapy, mercury levels in both different dose groups showed that mercury levels present in blood were significantly reduced and the symptoms also reduced. The mercury concentration of the diet had a significant effect on iron status as assessed by serum iron. Iron serum concentration is the lowest in the group having the highest mercury concentration which is probably due to a significant interference that could take place by mercury through iron uptake mechanism. It is clear that decrease in the iron level in the blood affect hematological indices such as hemoglobin, Red Blood Cells etc. (Table 3).

Presented data showed that the increasing doses of mercury caused a progressive increase in Total Iron Binding Capacity (TIBC). The significantly higher TIBC appeared in all groups receiving dietary mercury in comparison with the control group. The rate of transferrin saturation (TS) was subsequently calculated using the following equation: transferrin saturation (%)=serum Fe concentration (µg/L)/ TIBC (µg/L) × 100. The saturation of transferrin with iron ions depends on the presence of mercury in diet and was markedly lower in two groups that consume mercury in drinking water when compared with the control group. Also our results showed that the saturation of transferrin in blood at higher dose level of mercury was less than the lower dose level.

In this study, some other hematological indices such as Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), before and after chelation therapy were calculated. The MCV is calculated by dividing the total volume of packed red blood cells (also known as hematocrit) by the total number of Red Blood Cells (RBCs). The resulting number is then multiplied by 10. The mean corpuscular hemoglobin (MCH) is the average mass of hemoglobin per red blood cell in a sample of blood. Also in this case, the resulting number is then multiplied by 10. The mean corpuscular hemoglobin concentration (MCHC) is calculated by dividing the hemoglobin by the hematocrit. These three factors were decreased in this study in comparison with the control group. Decrease in MCHC is less than the MCV and MCH, because of the hemoglobin and hematocrit decrease with the same rate. The normal level of MCHC in iron deficiency anemia in most patients confirms this fact.

The Hematocrit (Ht or HCT), also known as Packed Cell Volume (PCV) or Erythrocyte Volume Fraction (EVF), is the volume percentage (%) of red blood cells in blood. Except serum iron and the percentage of transferrin saturation, the serum ferritin concentration has been used to assess iron status. Ferritin is the principal store of non-heme Fe in animals (most Fe is occupied in hemoglobin and myoglobin). The ferritin levels measured usually have a direct correlation with the total amount of iron stored in the body. Our results showed that the serum ferritin concentration and HCT were markedly lower in two groups that had consumed mercury in drinking water when compared with the control group. Also our results in Table 3 showed an increased platelet count and a marked increase in Total Iron-Binding Capacity (TIBC) when the other of hematological indices decreases.

After combination therapy with DFX and DFP that start immediately after mercury administration, mercury toxicity symptoms observed in rats have been removed in a short term after drug administration. The results of chelation therapy with DFX and DFP returns iron level to normal state. Therefore, all hematological indices that investigated in this study returned to normal state (control group values). On the other hand, at the end of the experimental period, all hematologic parameters studied in the control rats, namely Hb concentration, mean corpuscular volume, serum Fe, red blood cells, hematocrit, platelets, serum ferritin, transferrin saturation, TIBC, etc. were within normal limits in rats. The results of hematological indices after chelation therapy are summarized in Table 4.

Effects of chelation on mercury-induced toxicity

In order to investigate the effect of passing time in removing mercury from their body spontaneously, one group was treated without chelation therapy. The results of chelation therapy group are shown in Table 5. Comparison of the results obtained from both (with and without chelation therapy) groups are indicating that passing time has no significant effect on the removal of mercury. Combination therapy with DFX and DFP cause that the mercury level presented in blood serum significantly reduced and simultaneously, iron concentrations returned to the normal level and the symptoms of toxicity also were reduced. The results passed the t test at 95% confidence level and were significant.

Hematological indices	Control	Low dose drinking of mercury	High dose drinking of mercury
Serum iron (µg/dL)	138.65 ± 12.623	134.24 ± 10.245	137.44 ± 11.750
TIBC (µg/dL)	284.34 ± 23.18	280.15 ± 25.10	288.64 ± 25.22
TS (%)	47.521± 7.192	48.315 ± 8.200	46.350 ± 7.257
Serum ferritin (µg/L)	82.523 ± 2.711	82.125 ± 3.423	81.290 ± 3.105
Hemoglobin (g/dL)	14.790 ± 1.898	13.258 ± 1.124	14.880 ± 2.015
Platelet (10^9/L)	738.10 ± 52.21	730.24 ± 50.48	738.10 ± 52.21
RBCs (10^{12}/L)	7.100 ± 0.973	6.959 ± 0.750	7.210 ± 1.003
HCT (%)	40.810 ± 5.097	39.954 ± 5.170	39.750 ± 5.123
MCV (fL)	58.20 ± 1.21	57.45 ± 1.73	59.12 ± 1.45
MCH (pg)	20.980 ± 0.859	20.980 ± 0.859	20.980 ± 0.859
MCHC (g/dL)	36.250 ± 1.159	37.240 ± 1.459	36.145 ± 1.219

Table 4: Hematological indices in various groups of rats after DFX+DFP administration (Results are present as arithmetic means ± SEM, Significant at $p<0.05$ when compared with control).

Group	After mercury administration (µg/l)	Without DFX+DFP administration (µg/l)	With DFX+DFP administration (µg/l)
Control	1.575 ± 0.125(10)	1.413 ± 0.116(10)	0.405 ± 0.009(10)
Drinking (low level)	35.751 ± 4.125(10)	34.895 ± 2.249(10)	3.627 ± 0.275(10)
Drinking(high level)	55.817 ± 4.314(8)	53.025 ± 4. 746(7)	1.875 ± 0.205(8)

Table 5: Mercury concentration (µg/l) in blood serum of various groups of rats after mercury and with and without DFX+DFP administration (Results are present as arithmetic means ± SEM, number of animals in parenthesis. Significant at $p<0.05$ when compared with control).

Discussion

Chelation therapy is the administration of chelating agents to remove heavy metals from the body. Chelation therapy has a long history of use in clinical toxicology. The term 'chelation therapy' usually refers to the use of proligands as drugs to treat disorders resulting from the presence of unwanted metal ions arising from intoxication or disease. To be effective, the proligand must complex and sequester the target metal ion then promote its excretion and removal from the body in complexed form without impairing the normal biochemistry of metals in vivo. Consequently the proligand used must be selective for the target metal ion so as not to remove other biologically important metals. In cases where a biologically essential metal such as iron or copper is the target, the sequestering agent must not compete with any natural binding sites for the target metal to the extent that it compromises normal function and health. However, where nonessential toxic metals are involved the sequestering agent may need to compete with natural metal binding sites to prevent uptake of the target metal ion [24]. Recent studies have focused on the distribution of some toxic metals like mercury and its interaction with essential trace metals such as iron. Toxic elements cause anemia by impairment of heme synthesis and increased rate of red blood cell destruction [25-27]. Heme is prosthetic groups containing iron centre in hemoglobin and myoglobin. In summarize, mammals and most other animals and plants, special proteins such as myoglobin and hemoglobin contain an iron (Fe) porphyrin cofactor [28]. Anemia is a pathologic process in which the hemoglobin (Hb) concentration in red blood cells is abnormally low. On the other hands, anemia is a decrease in number of red blood cells (RBCs) or less than the normal quantity of hemoglobin in blood. According to our results, we believe that mercury effects on the hematological system result in inhibition of heme synthesis. Therefore it is possible that iron deficiency as observed in the present study, which is a proven cause of anemia, leads to an increased absorption of mercury in the body, resulting in high blood mercury levels. There is no doubt that iron (Fe) deficiency is the cause of most forms of anemia. Iron-deficiency anemia is characterized by the reduction or absence of Fe stores, low serum concentrations of Fe and (hemoglobin) Hb, decreased hematocrit, an increased platelet count [6], a low rate of Transferrin Saturation (TS), low serum ferritin, and a marked increase in Total Iron-Binding Capacity (TIBC). Consequently, diagnosis of iron deficiency in most patients can be made based on the measurement of a low serum iron and low serum ferritin with an elevated Total Iron Binding Capacity (TIBC). Also Mean Corpuscular Volume (MCV), mean corpuscular hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC), Hematocrit (HCT), Red Blood Cells (RBCs), Hemoglobin (Hb), and percentage of Transferrin Saturation (TS) values decreased while platelet count increased.

Our results prove the harmful effect of mercury on iron metabolism in rats. Dietary mercury, consumed in amounts of 40 mg Hg^{2+}/kg body weight (Low dose drinking of mercury) and 80 mg Hg^{2+}/kg body weight (High dose drinking of mercury) caused a decrease in apparent absorption of iron and it was accompanied by a decrease in iron concentration in blood serum and a development of anemia. Our results in Table 3 confirmed the iron deficiency anemia in rats.

The aim of this study was to test the chelation potency of DFX and DFP given to animals after mercury administration. This kind of therapy by combining two cultures is based on the assumption that various chelating agents mobilize toxic element from different tissue compartments and therefore better results are expected. Also another benefit of combination therapies is that combining two chelators reduce side effects of these drugs [29]. The results of chelation therapy with DFX and DFP return iron level to normal state. Therefore all hematological indices that investigated in this study returned to normal state (control group values). On the other hand, at the end of the experimental period, all hematologic parameters studied in the control rats, namely Hb concentration, mean corpuscular volume, serum Fe, red blood cells, hematocrit, platelets, serum ferritin, transferrin saturation, TIBC, etc. were within normal limits in rats. Also iron deficiency anemia that caused by mercury administration obviated.

Our results showed that this procedure might be useful for preliminary testing of the efficiency of chelating agents in removing mercury. Even though their toxicities are relatively low, basic pre-clinical research is needed before they could be recommended for human administration.

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