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Chelation of cadmium by combining deferasirox and deferiprone in rats

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Abstract

The present research aimed to characterize the potential efficiency of two chelators after cadmium administration for 60 days following two dose levels of 20 and 40 mg/kg body weight daily to male rats. However, the hypothesis that the two chelators might be more efficient as combined therapy than as single therapy in removing cadmium from the body was considered. In this way, two known chelators deferasirox and deferiprone (L₁) were chosen and tested in the acute rat model. Two chelators were given orally as a single or combined therapy for the period of a week. Cadmium and iron concentrations in various tissues were determined by graphite furnace and flame atomic absorption spectrometry methods, respectively. The combined chelation therapy results show that Deferasirox and L₁ are able to remove cadmium ions from the body while iron concentration returned to the normal level and symptoms are also decreased.

Keywords

Chelation therapy, deferasirox, deferiprone, cadmium, iron

Introduction

Cadmium (Cd), as a well-known environmental hazard, exerts a number of toxic effects in human and animal organisms. Other cellular activities would be differentiated by Cd cell proliferation effects (Waisberg et al., 2003). Cd can also enter the aquatic environment naturally from rocks and soils directly exposed to surface water. They can be concentrated from the water and sediments into aquatic mammals (Henkel and Krebs, 2004; Huang et al., 2004). Many studies have examined the bioaccumulation and toxic responses of Cd in animals, plants, phytoplankton and freshwater bacteria (Fatemi et al., 2009; Hassler and Wilkinson, 2003; Miao et al., 2005; Mirimanoff and Wilkinson, 2000; Waisberg et al., 2003; Wilde et al., 2006). A number of Cd-induced effects including deterioration of cell-cell adhesion, DNA-related processes, cell signaling and energy metabolism can imply that this metal acts on the different molecular targets in human organism. It is shown that Cd can induce apoptosis in mouse liver (Fatemi et al., 2009; Ivanoviene et al., 2004; Shimoda et al., 2001). Cd in liver moves to kidneys where it is excreted and then re-absorbed almost entirely. This poor ability of

humans to excrete Cd through kidneys underlies the health implications of Cd as a nephrotoxin (Akesson et al., 2005; Satarug et al., 2006). In long-term high-exposure cases, the hypertension has been understood to arise secondary to the loss of kidney's function. A number of active genes in the kidneys are related to the control of blood pressure in physiologic state, however, including those affecting salt excretion and re-absorption, vascular tone and volume homeostasis (Lifton et al., 2001), and it is plausible that even low-level exposure to Cd may affect the blood pressure control of human body. However, few studies supported the role of Cd-induced nephropathy including

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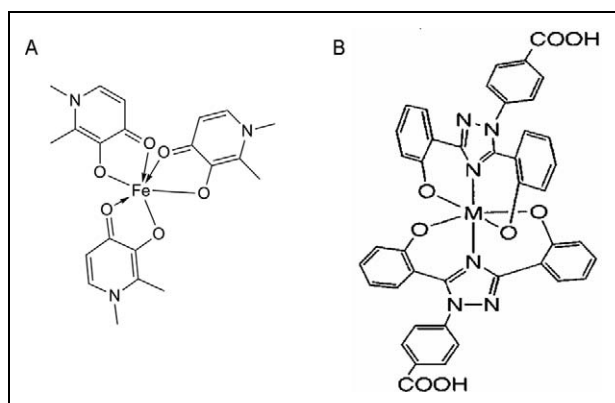


Figure 1. Chemical structures of deferiprone (A) and deferasirox (B).

tubular damage, which might induce increase of blood pressure in part. If the kidney's role in the control of blood pressure is affected by Cd, then the kidney function may act as an effect modifier on the association between Cd exposure and hypertension (Satarug et al., 2005). One way to remove toxic elements, such as Cd, from the body is chelation therapy. Chelation therapy involves the use of ligating drugs that bind metal for the treatment of potentially fatal conditions. These ligands promote the excretion and subsequent depletion of this transition metal in biological systems. Clinical evaluations of some chelators for removal of toxic metal ions in rats have been previously reported by Fatemi et al. (Amiri et al., 2007; Fatemi et al., 2007; 2009; Shokooh Saljooghi and Fatemi, 2010b, c; Tubafard and Fatemi, 2008; Tubafard et al., 2010). These chelating agents consist of a range of bidentate, tridentate and hexadentate ligands in which two, three or six atoms are able to coordinate, respectively (Clarke and Martell, 1992; Gomez et al., 1988). In this procedure, chelator is added to the blood through a vein or administered orally in order to remove toxic element. Deferasirox (4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic acid, or ICL670; Figure 1) was first reported in 1999 (Heinz et al., 1999). It is a tridentate chelator with high selectivity for Fe^{3+} , and its NO_2 donation arises from one triazole nitrogen and two phenolate oxygen donors. It selectively binds Fe^{3+} over Fe^{2+} and shows little affinity for other divalent ions such as Zn^{2+} or Cu^{2+} (Steinhauser et al., 2004). 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 (Nisbet-Brown et al., 2003). In 2005, deferasirox became the first FDA-approved oral alternative for

treatment of iron overload and was subsequently approved in the EU in 2006 (Yang et al., 2007). A simple synthesis of a chelator L_1 (deferiprone; 1, 2-dimethyl-3-hydroxypyridin-4-one; Figure 1) for iron overload has been described. L_1 is water soluble and can be given orally (Kontoghiorghes and Sheppard, 1987). This kind of therapy by combining two chelators is based on the assumption that various chelating agent mobilize toxic element from different tissue compartments and therefore better results are expected (Flora et al., 1995). Results of this kind of combined chelation therapy has been confirmed by Fatemi et al. (Amiri et al., 2007; Fatemi et al., 2007, 2009; Tubafard et al., 2010; Tubafard and Fatemi, 2008). The aim of this study was to test the chelation potency of deferasirox and L_1 in combination, given to animals after Cd loading. Testing was performed by using an acute experimental model on rats with individual or combined chelators given shortly after Cd application.

Experimental section

Apparatus

Atomic absorption spectrometer (F AAS and GF AAS) Model Varian was used for measurement of Cd and iron concentrations in organs, respectively.

Maintenance of the animals

Male Wistar rats were obtained from Razi Institute (Karaj, Iran). They bred in animal house at Kerman Neuroscience Research Center, Kerman, Iran. The rats were maintained under a controlled light: dark (12: 12 h) schedule at $23^\circ\text{C} \pm 1^\circ\text{C}$ and humidity of 55%. The animals were assigned randomly to control and treated groups and were kept in well-cleaned sterilized cages. The rat food was purchased from Razi Institute. This study was approved by the ethics committee of Shahid Bahonar University of Kerman, Kerman, Iran and Kerman Neuroscience Research Center, Kerman, Iran.

Materials

L_1 and other materials were purchased from Merck Chemicals Co. and deferasirox was purchased from Novartis Co. (Basel, Switzerland).

Methods

In our model, we used two different doses of Cd followed by an early administration of chelating agent.

Table 1. Body weights over 60 days for rats in different groups (values are mean for the number of observation in parentheses)

Group	Control	Low dose drinking of cadmium	High dose drinking of cadmium
Initial body weight ^a (g)	205 ± 7(5) (day 1)	200 ± 4(5) (day 1)	195 ± 3(5) (day 1)
Final body weight ^a (g)	275 ± 7(5) (day 60)	255 ± 8(5) (day 67)	225 ± 7(4) (day 67)

^a Main of five determination ± standard deviation.

Table 2. Classification of animals

Control group			
All rats	Drinking group	Low level drinking group; 20 mg/kg body weight	Before chelation therapy Without chelation therapy Chelation therapy with Deferasirox (140 mg/kg body weight) Chelation therapy with L ₁ (300 mg/kg body weight) Chelation therapy with deferasirox (70 mg/kg body weight) + L ₁ (150 mg/kg body weight)
		Low level drinking group; 40 mg/kg body weight	Before chelation therapy Without chelation therapy Chelation therapy with deferasirox (140 mg/kg body weight) Chelation therapy with L ₁ (300 mg/kg body weight) Chelation therapy with deferasirox (70 mg/kg body weight) + L ₁ (150 mg/kg body weight)

Abbreviation: L₁: deferiprone.

Experiments were performed on 7-week-old Wistar male rats.

There were slight differences between the groups in the initial body weight of the rats (mean 200 g), but at the end of Cd administration experiment, those given Cd in their diet had significant weight loss (Table 1). Comparison of the weights in this experiment shows dietary treatment affected the food intake, whereby animals given normal diet consumed more food than those given Cd. Also because of the slight (but significant) differences in body weight of rats at the start of study, the results can be influenced by the initial classification and assignment of rats to treated groups. Therefore, the day 1 groups' body weights are notable and they must be considered. Consequently after acclimatization of animals, we assigned them randomly to control and treated groups.

Cd at two doses of 20 and 40 mg/kg body weight were given to animals for 60 days. Chelation therapy was carried out after Cd application.

In this part of work, animals were divided into four groups, control, deferasirox, L₁ and Deferasirox + L₁ (Table 2). Chelators were given after Cd application. Chelators were given orally (Deferasirox) and intraperitoneally (L₁) in the volume of 0.5 mL as mono

or combined therapies. Doses of Deferasirox and L₁ were 70 and 150 mg/kg body weight, respectively (Table 2). Chelators were given immediately after Cd application during 1 week. Cd toxicity symptoms observed in rats have been removed in short term after drug administration. After chelation therapy, these rats were anesthetized with ether vapors and immobilized by cervical dislocation. Animals were sacrificed by exsanguinations from abdominal aorta; and kidneys, intestine, testicles, liver and heart samples were collected, weighed and dried for determination of Cd content. The samples were placed in an oven at 60°C for 3 days. They were then digested by 1.5 mL of HNO₃ per 1 g of dry weight. After digestion, the solutions were evaporated with the addition of 1.0 mL of H₂O₂ under the hood. Then, the residue was diluted with water to 100 mL volume.

Results

Results of Cd raising and iron reduction in organs of two Cd doses groups were statistically different. The Cd accumulation in tissues at 40 mg/kg dose was more than the group at 20 mg/kg. A significant difference between control and treatment groups was

Table 3. The result of cadmium level before and after chelation therapies^a

Group	Before chelation therapy	Without chelation therapy	Chelation therapy with deferasirox	Chelation therapy with L ₁	Combination
Heart (mg/kg)					
Control	0.024 ± 0.008	0.023 ± 0.007			
Drinking (low dose)	0.112 ± 0.013	0.110 ± 0.019	0.069 ± 0.011	0.083 ± 0.014	0.044 ± 0.018
Drinking (high dose)	0.236 ± 0.017	0.225 ± 0.021	0.089 ± 0.015	0.110 ± 0.016	0.067 ± 0.017
Kidneys (mg/kg)					
Control	0.034 ± 0.004	0.032 ± 0.005			
Drinking (low dose)	0.561 ± 0.034	0.533 ± 0.014	0.300 ± 0.022	0.207 ± 0.016	0.137 ± 0.013
Drinking (high dose)	0.911 ± 0.018	0.879 ± 0.023	0.308 ± 0.017	0.239 ± 0.013	0.172 ± 0.013
Liver (mg/kg)					
Control	0.039 ± 0.007	0.038 ± 0.006			
Drinking (low dose)	0.354 ± 0.018	0.338 ± 0.044	0.162 ± 0.019	0.202 ± 0.015	0.093 ± 0.019
Drinking (high dose)	0.753 ± 0.012	0.741 ± 0.016	0.259 ± 0.021	0.329 ± 0.012	0.147 ± 0.016
Intestine (mg/kg)					
Control	0.041 ± 0.024	0.039 ± 0.015			
Drinking (low dose)	0.453 ± 0.012	0.441 ± 0.016	0.283 ± 0.021	0.365 ± 0.017	0.189 ± 0.013
Drinking (high dose)	0.524 ± 0.021	0.516 ± 0.018	0.351 ± 0.019	0.425 ± 0.012	0.239 ± 0.016

Abbreviation: L₁: deferiprone.

^a The number of rats in each group were five; results are represented as arithmetic means ± SEM, significant at $p < 0.05$ when compared with control.

observed. The general symptom of toxicity appeared after 60 days of administration of Cd.

Abnormal clinical signs in animals were observed as follows: darkening of the eyes, yellowish discoloration of hair, flaccid and hypotonic muscles, irritability, weakness and loss of hair. Also the body weights of all animals were significantly decreased. The highest amount of Cd was found in kidneys followed by liver.

After the chelation therapy, the iron and Cd levels in both different doses groups showed that Cd levels present in all tissues were significantly reduced whereas, iron concentration returned to the normal level and the symptoms also reduced. Iron level is lowest in the group having the highest Cd concentration, which is probably because of a significant interference that could take place by Cd through iron uptake mechanism. Interactions between Cd and iron have previously been reported (Shokooh Saljooghi and Fatemi, 2010a). There is statistical difference between Deferasirox and L₁ in reducing the amount of Cd in liver. The *t*-test was applied to the results assuming the certified values are the true values.

At both lower and higher doses, deferasirox + L₁ groups were more effective than L₁ or deferasirox. When comparing mono efficiencies of chelators in this experiment, deferasirox was more efficient in decreasing Cd concentration in tissues apart from kidneys, whereas, L₁ was to be more efficient in kidneys.

Comparison of mono and combining chelators in this experiment shows more efficiency of deferasirox + L₁ in reducing the Cd level in all tissues. The results of organ distribution of Cd before and after chelation therapies for Cd are shown in Table 3.

Furthermore, iron concentration after administration of Cd was significantly decreased. The difference between iron values before and after chelation therapy is notable. Combination of deferasirox + L₁ shows more efficiency in returning iron level to normal state. The results of iron concentrations before and after chelation therapies are summarized in Table 4.

In order to investigate the effect of passing time in removing Cd from the body spontaneously, one group was treated as without chelation therapy. The results of chelation therapy group are shown in Tables 3 and 4. Comparison of the results obtained from both (with and without chelation therapy) groups are indicating that the passing time has no significant effect on removal of Cd.

Discussion

Chelation therapy is one of the most effective ways to remove toxic elements from the biological system. There has been an increase in Cd exposure because of its presence in fertilizers and sewage sludge and also its increased industrial use in Cd-Ni batteries. Although there are a number of reports on

Table 4. The result of iron level before and after chelation therapies

Group	Before chelation therapy	Without chelation therapy	Chelation therapy with Deferasirox	Chelation therapy with L ₁	Combination
Heart (mg/kg)					
Control	6.36 ± 0.12	6.32 ± 0.11			
Drinking (low dose)	5.25 ± 0.21	5.31 ± 0.18	6.00 ± 0.19	5.65 ± 0.19	6.74 ± 0.17
Drinking (high dose)	3.96 ± 0.23	3.89 ± 0.23	6.12 ± 0.12	5.45 ± 0.15	6.43 ± 0.16
Kidneys (mg/kg)					
Control	5.56 ± 0.17	5.54 ± 0.12			
Drinking (low dose)	4.15 ± 0.19	4.19 ± 0.17	5.25 ± 0.14	4.12 ± 0.17	6.51 ± 0.19
Drinking (high dose)	2.68 ± 0.22	2.79 ± 0.19	5.34 ± 0.22	4.03 ± 0.14	6.12 ± 0.13
Liver (mg/kg)					
Control	5.73 ± 0.15	5.85 ± 0.15			
Drinking (low dose)	4.32 ± 0.21	4.21 ± 0.12	4.97 ± 0.18	3.12 ± 0.15	5.85 ± 0.15
Drinking (high dose)	2.94 ± 0.18	3.00 ± 0.17	4.95 ± 0.19	3.45 ± 0.18	5.34 ± 0.19
Intestine (mg/kg)					
Control	4.32 ± 0.14	4.45 ± 0.13			
Drinking (low dose)	2.35 ± 0.18	2.39 ± 0.18	2.96 ± 0.17	3.53 ± 0.17	4.77 ± 0.15
Drinking (high dose)	1.66 ± 0.15	1.70 ± 0.14	3.01 ± 0.21	3.91 ± 0.17	4.56 ± 0.11

Abbreviation: L₁: deferiprone.

The number of rats in each group were five; results are represented as arithmetic means ± SEM, significant at $p < 0.05$ when compared with control.

occupational and environmental exposures to Cd compounds, treatment of Cd poisoning has been difficult because there is neither a safe practical means of evaluating bioavailability body burden nor is there a recommended therapeutic chelating agent for chronic Cd intoxication (Jones and Cherian, 1990). The therapeutic effects of various chelating agents including 2, 3-dimercaptopropanol (BAL) and its soluble glycosides have been studied without much success in acute Cd intoxication (Dalhamn and Friberg, 1955). The aim of the present work was to evaluate the ability of deferasirox + L₁ in removing Cd from the body. Many studies have now reported the high absorption/distribution, long-term efficacy and safety of deferasirox and L₁ in removing some toxic metal ions and treating iron overload in patients with β -thalassaemia major (Cappellini, 2008; Neufeld, 2006; Wood et al., 2006). In this investigation, a short-term experimental model was used in order to speed up the preliminary testing procedure. The effect of chelator on Cd and iron level was remarkable. It has been reported that the chelating agents having higher stability constants with a metal in aqueous solution may also prove successful in reducing the body burden of the metal (Kaur et al., 1984). Gastrointestinal absorption and uptake of Cd after oral exposure shows the accumulation of Cd in different organs as well as decrease of iron concentration in different tissues. In order to

understand the abilities of mentioned chelators, we have done the distribution of Cd and observed accumulation of direct toxic effect of Cd in the liver and other tissues. After administration of chelating agents, the Cd content returned to nearly normal level of control group, which indicates that deferasirox + L₁ effectively increases the elimination of Cd in rats and the symptom was greatly decreased. A comparison of the results obtained from with and without Chelation therapies indicate that combined (deferasirox + L₁) therapy increases the elimination of Cd effectively, so, removal of Cd is not time dependent at all, also toxicity and side effects of deferasirox and L₁ are very low, therefore after basic preclinical research, they could be recommended for human administration.

In comparison to the results obtained by Fatemi et al. (Fatemi et al., 2007; Amiri et al., 2007; Tubafard and Fatemi, 2008; Fatemi et al., 2009; Tubafard et al., 2010) and our present results, it can be concluded that the two chelators (deferasirox + L₁) are more efficient as combined therapy than single therapy in removing Cd from all tissues.

Therefore deferasirox + L₁ could eliminate Cd from rat organs and treat side effects and general symptoms of toxicity caused by Cd.

Thus deferasirox + L₁ represent a promising drug of Cd-mobilizing agent. Our results showed that this procedure might be useful for preliminary testing of

the efficiency of chelating agent in removing Cd. 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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