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The efficacy of deferiprone on tissues aluminum removal and copper, zinc, manganese level in rabbits

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Abstract

The effect of 1,2-dimethyl-3-hydroxypyrid-4-one [deferiprone (DE)] on aluminum mobilization and elimination from tissues and serum as well as the influence on the excretion of trace elements, copper, zinc and manganese in rabbits was investigated. Sixteen New Zealand rabbits were randomly divided into three groups: control, Al-only and Al + DE. The Al-only and Al + DE animals received injections of $Al_2(SO_4)_3 \cdot 18H_2O$ 600 μmol Al/kg 5 days per week for 3 weeks. One week after the last Al injection the Al + DE rabbits were given deferiprone 750 μmol/kg/day intragastrically for 2 weeks. At the 42nd day the animals were sacrificed and the organs were taken and digested. Blood was taken from the ear artery three times (at the initiation of the experiment, before and after deferiprone administration). The aluminum and copper, zinc, manganese were determined by atomic absorption spectrophotometry. Our results showed that deferiprone could highly mobilize aluminum stores from tissues. At the end of experiment the aluminum contents of bone, kidney, liver and brain in Al + DE were significantly lower than that in Al-only rabbits. The copper, zinc, manganese contents were not affected by deferiprone administration.

Keywords: Aluminum; Deferiprone; Trace elements; Rabbits

1. Introduction

Aluminum enters into the body from the environment and from diet and medication. However, a number of toxic effects have been described, which could be due to an accumulation of aluminum in the organs [1–4]. Substantial evidence suggests that dialysis encephalopathy syndrome (DES) is caused by aluminum intoxication [5]. Aluminum has also been implicated as a possible contributing factor in senile dementia of the Alzheimer type [6,7]. Although reduction of aluminum intake in renal impaired people to the minimally effective dose is advisable, aluminum can not be totally avoided due to its ubiquitous distribution in food, water and environment [8]. So far, the only treatment available against it has been desferrioxamine (DFO), which induces major side effects [9]. A previous study demonstrated that subcutaneously injected DFO increased serum aluminum concentration and tissue aluminum elimination in Al-loaded rats. However, its use is limited to a small proportion of the patients [10]. Because it is expensive and inactive, when given orally or as a suppository [11,12]. The use of DFO in dialysis patients is not free from side-effect. In some patients, ocular toxicity, disturbances of colour vision and loss of hearing have been described [13]. So a cheap, orally active and non-toxic aluminum chelator is needed. 1,2-dimethyl-3-hydroxypyrid-4-one [deferiprone (DE)] is a member of the

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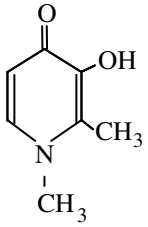
hydroxypyridinones family with the molecular weight 139 Da. By virtue of its low molecular weight, deferiprone possesses high absorption efficiency and it is efficiently absorbed from the human intestinal tract. Deferiprone was originally synthesized by Robert Hider and his colleagues at Essex University, as an alternative to desferioxamine in the treatment of iron overload [14].

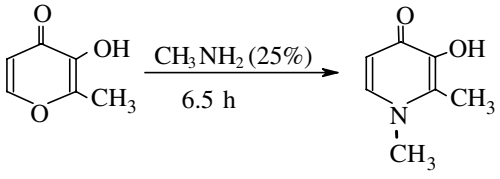


Aluminum and iron are hard acids with similar ionic radii (54 and 64 pm). They bind to the same plasma proteins. One study suggested that oral administration of deferiprone was an effective treatment in enhancing urinary Al excretion of Al-loaded rats. This beneficial effect was similar for old and young animals [15]. In present study, a controlled experiment in rabbits was conducted to determine if the chelating agent deferiprone could mobilize aluminum from tissues and increase aluminum elimination, as well as influence the excretion of trace elements copper, zinc and manganese.

2. Materials and methods

2.1. Materials and animals

Aluminum sulfate ($Al_2(SO_4)_3 \cdot 18H_2O$) was obtained from Shanghai Chemistry Factory. 1,2-dimethyl-3-hydroxypyrid-4-one was synthesized by our department. The route of synthesis of deferiprone is



THERMO ELEMENTAL GF95Z-M6 atomic absorption spectrophotometer was used. New Zealand white rabbits were supplied by the animal center of our university. The animals, housed in stainless steel floor cages, had free access to water (Al = 12 μg/L) and stripe diet (Al = 40 μg/g). Animals were weighed five times a week.

2.2. Treatments of rabbits

Sixteen New Zealand white rabbits were randomly divided into three groups: control ($n = 5$, 2.5 ± 0.2 kg), Al-only ($n = 5$, 2.6 ± 0.4 kg) and Al + DE ($n = 6$, 2.5 ± 0.2 kg), Al-loaded rabbits received 600 μmol Al/kg/day (as the sulfate) five times weekly for 3 weeks by sc injection into random sites in a 5×7 cm area of the back. Controls received 15 sc injections of sterile saline water. The total aluminum dose per rabbit was of 243 mg/kg. One week after the last injection the Al + DE rabbits were given the dose of deferiprone (750 μmol/kg/day) intragastrically for 2 weeks. This procedure resulted in a total sum of 1460 mg/kg, while control and Al-only rabbits received a sham treatment of sterile saline water.

2.3. Preparation of tissue and blood samples

At the 42nd day, the animals were sacrificed and the selected organs (brain, liver, left kidney and bone) were removed, weighed, and frozen for later analysis of aluminum, copper, zinc and manganese content. The blood were taken from the ear artery three times (at the initiation of the experiment, before and after deferiprone administration).

2.4. Chemical analysis

Aluminum, copper and manganese were performed by graphite furnace atomic absorption spectrophotometry. Zinc was determined by flame atomic absorption spectrophotometry. The parameters of the absorption spectrophotometer were shown in Table 1.

Glassware and plasticware were cleaned in 20% nitric acid before use.

Samples from soft tissues and bone were digested with HNO_3 and $HClO_4$ for 4 h at a temperature of 100 °C, and the temperature was raised to 180 °C for another 4 h. The remaining acids were volatilized at 200 °C until white residues appeared. The residues were dissolved in deionized water and made up to a suitable volume. The serum was direct diluted with 0.5%

Table 1
The parameters of the absorption spectrophotometer

Elements	Lamp current (mA)	Slit (nm)	Wave length (nm)	Flame type (L/min)	Acetylene flow (L/min)	Air flow (L/min)	Background correction
Zn	75%	0.5	213.9	Air/acet	1.2	13.5	Closed
Cu	75%	0.5	324.8	Graphite furnace	–	–	Zeem
Mn	75%	0.2	279.5	Graphite furnace	–	–	Zeem
Al	75%	0.5	309.3	Graphite furnace	–	–	Zeem