J.Sci.I.R.Iran

Vol. 1, No. 5
Autumn, 1990

# THE RELATIONSHIP BETWEEN ALUMINIUM TOXICITY AND IRON METABOLISM IN RATS

A. A. Moshtaghie, M. Ani and M. Taher

*Department of Biochemistry, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran*

**Abstract**

The relationship between aluminium toxicity and iron metabolism was studied. Male rats were exposed to aluminium by daily intraperitoneal injection of 40 μmole/kg body weight. After 45 days, aluminium intoxified rats had a significant lowered serum ferritin (55%), iron (42%), TIBC (25%) and hemoglobin (31%). At the same time the serum ceruloplasmin level was elevated by 60%. This result shows that aluminium interferes with the iron metabolism in rats and might be considered as a possible cause of hypochromic microcytic anemia which is found following regular hemodialysis in chronic renal failure patients.

## Introduction

It is now well documented that aluminium transfers across the dialysis membrane, enters blood circulation and binds to serum transferrin in chronic renal failure patients treated by long term intermitent hemodialysis [1, 2]. Transferrin is a single chain $\beta_1$- glycoprotein responsible for the transportation of iron in blood circulation [3].

In 1978 Elliot and McDougall described anemia in 6 patients with dialysis osteodystrophy and with dialysis encephalopathy [4]. They suggested that a possible casual relationship may exist between anemia and aluminium intoxication in patients on hemodialysis [5]. The major aim of the present study was to investigate the effect of aluminium on iron metabolism by determining some biochemical factors related to iron metabolism including serum iron, TIBC, ferritin, ceruloplasmin and hemoglobin in rats.

## Methods and Materials

Male Wister rats weighing 200- 250 gr were used for all experiments. Animals were maintained on food and water *ad libitum*. Rats were injected daily, intraperitoneally with lmg/kg aluminium as $AlCl_3$ in 0.1 ml of saline. On the date of examination animals were anaesthetized and blood was withdrawn from their hearts. Serum was then separated from whole blood by centrifugation at 2000 rpm using universal bench centrifuge.

Hemoglobin was determined by the method reported by Fairbanks [6], serum iron and TIBC were determined using Phenanthroline as a chromogen [7] and ferritin was measured by immunoradiometic assay using laboratory kits purchased from Diagnostic Products Corporation (Los Angles, CA 90045).

The concentration of ceruloplasmin in serum was estimated on the basis of its oxidase activity using paraphenylendiamine dihydrochloride as the substrate and the absorbance was measured at 525 nm with a Perkin- Elmer Spectrophotometer (UV/ Vis model 551S) [8].

## Results

The effect of aluminium on serum levels of iron, TIBC, ferritin, hemoglobin and ceruloplasmin is shown in Table 1.

The results show that there is a significant reduction in iron concentration (42%, $P < 0.001$) following aluminium treatment. This is accompanied by 25% reduction in TIBC ($p < 0.001$). The levels of ferritin and hemoglobin were also lowered in treated animals by 55 and 31 percent respectively ($P < 0.005$). Ceruloplasmin activity, on the other hand, showed a significant elevation (66%, $P < 0.001$).

**Key words:** Aluminium, Iron, Heme, TIBC, Ferritin, Ceruloplasmin

**Table 1: Serum iron, TIBC, ferritin, hemoglobin and ceruloplasmin levels in aluminium overload rats compared with those of control animals. Values are Mean ± SE of 5 separate experiments.**

| Factors / Animals | Iron (μg/dl) | TIBC (μg/dl) | Ferritin (μg/gl) | Hb (g/dl) | Ceruloplasmin (mg/dl) |
|---|---|---|---|---|---|
| Control | 120.2±1.22 | 385.08±1.65 | 38.2±1.44 | 15.86±0.38 | 28.09±2.47 |
| Experimentals | 70.1±3.07 | 292.01±1.07 | 17.3±1.13 | 11.00±1.13 | 47.5±2.73 |

## Discussion

Patients with chronic renal failure maintained on regular hemodialysis suffer from hypochromic microcytic anemia [9] which is related to either the presence of aluminium in dialysis fluid or aluminium phosphate binders taken by these patients for reducing hyperphosphatemia [10]. We have previously shown that aluminium binds to serum transferrin and may interfere with iron metabolism particularly in heme synthesis [11]. When rat mitochondria were incubated with $^{55}$Fe- transferrin and $^{55}$Fe- Al- transferrin, there was a significant reduction in heme synthesis in the presence of deutroporphyrin as substrate for ferrochelatase activity [12]. Quantitative measurements of aluminium in human red blood cells showed that a significant amount of aluminium was accumulated in the cells [13]. The results of the present study are in good agreement with the observations of Touam et al [14] that aluminium reduces hemoglobin concentration. In addition, we have demonstrated that serum TIBC and ferritin were also reduced in aluminium intoxicated animals. The binding of aluminium to rat and human brain ferritin has already been reported by Fleming [15]. Spectrophotometric titration of apotransferrin with iron in the presence of aluminium showed a significant reduction in iron uptake by ferritin [12]. The reduction in ferritin level might be due to the replacement of Fe (III) by Al (III) in this molecule. It could be concluded that competition between aluminium and iron binding to serum transferrin may lead to the reduction in serum iron content, TIBC and ferritin concentration. The elevation of serum ceruloplasmin might be considered as a compensatory device in order to accelerate the oxidation of iron for binding either to transferrin or ferritin for heme synthesis.

## References

1. G. A. Trapp plasma aluminium is bound to transferrin. *Life Science* **33**: 311- 316 (1983).
2. A. A. Moshtaghie and A. W. Skillen, Binding of aluminium to transferrin and lactoferrin *Biochem. Soc. Trans.* **15**: 916- 917 (1986).
3. J. H. Brock, transferrins: Metaloproteins, P. M. Harrison ed., Macmillan, London, Vol. 11, pp 183- 262 (1985).
4. H. L. Elliot and A. I. MacDougal, Aluminium studies in dialysis encephalopathy. *Proc. Eur. Dial. Transplant Assoc.* **15**: 154- 163 (1978).
5. H. L. Elliot, A. I. MacDougal and G. S. Fell. Dialysis encephalopathy evidence implicating aluminium toxicity. *Dial. Transpl.* **9**: 1027- 1030 (1980).
6. V. F. Fairbanks, Hemoglobin, Hemoglobin derivatives and myoglobin in: Fundamentals of clinical chemistry ed. N. W. Tietz Saunders company, Philadelphia, second edition PP: 408- 411 (1982).
7. H. Varley, A. H. Gowenlock and B. Maurice, practical clinical Biochemistry, William Hein- emann medical books, London, Vol. 1, PP: 935- 937 (1984).
8. Kachmar J. F; Moss. D. W., In Fundamentals of Clinical Chemistry (ed. Tietz N. W) Saunders. W. B. Company Philadelphia pp 649- 652 (1976).
9. M. R. Wills and J. Savary, Aluminium Poisoning, Dialysis encephalopathy, Osteomalacia and Anemia *Lancet* **11**: 29- 33 (1983).
10. M. K. Ward, T. G. Feest, H. A., Ellis, I. S. Parkinson, D. N. Skerr, J. Herrington and G. L. Goode. Osteomalacic dialysis osteodystrophy, evidence for a waterborne aetiological agent, probably aluminium *Lancet* **1**: 841- 843 (1978).
11. A. W. Skillen and A. A. Moshtaghie, The binding of aluminium by human transferrin and the effect of desferroxamine: An equilibrium dialysis study in: Aluminium and other trace elements in renal disease, A. W. Taylor ed. Bailliere Tindall, London PP: 81- 85 (1986).
12. A. A. Moshtaghie, Ph. D. Thesis, Interrelationship between aluminium and iron metabolism in man, The University of Newcastle Upon Tyne, England (1988).
13. A. A. Moshtaghie and A. W. Skillen, Aluminium uptake by human erythrocytes: effect of glucose (abs.) *J. Trace. elements in Experimental Medicine* **2**: 110 (1989).
14. M. Touam, F. Martinz, B. Lacour, R. Bourdon, V. Zineyraff, S. D. Giubo and T. Drueke, Aluminium induced reversible microcytic anemia in chronic renal failure. *Clin. Nephrology* **19** 295- 298 (1983).
15. J. Fleming and J. G. Joshi, Brain ferritin and aluminium. *The FABES Journal* **2**(4): A 766 (1988).