

THE EFFECT OF ALUMINUM ON BIOCHEMICAL PARAMETERS RELATED TO BONE METABOLISM. A MODEL STUDY OF HEMODIALYSIS PATIENTS

A.A. MOSHTAGHIE, AND M. ANI

From the Dept. of Biochemistry, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Islamic Republic of Iran.

ABSTRACT

The influence of aluminum on some serum parameters related to bone metabolism has been investigated by daily administration of aluminum over different periods of time. Daily administration of aluminum (1 mg/kg BW) for 20 or 50 days elevated serum phosphorous concentration by 16 percent and had no significant effect on serum calcium level. When aluminum was injected as a complex with citric acid (1:1) there was a 22 percent elevation in serum phosphorous concentration, but again had no significant effect on serum calcium. Same amounts of aluminum caused a 28 percent elevation in serum alkaline phosphatase (ALKP), but had no significant effect on serum parathormone (PTH) either with or without citric acid. A marked reduction (about 41 percent) in serum calcitonin was observed when rats were given aluminum with or without citric acid. The relationship between aluminum toxicity and osteomalacia has been discussed.

MJIRI, Vol. 6, No. 2, 143-145, 1992

INTRODUCTION

Aluminum, the most prevalent metal in the earth's crust, has been implicated as an etiological factor in a variety of clinical disturbances in chronic renal failure who are maintained on regular hemodialysis. On the other hand, due to the high concentration of serum phosphate in these patients, they have to use aluminum phosphate binders in order to prevent hyperphosphatemia.¹ Aluminum from either dialysis fluid or aluminum phosphate binders enters blood circulation where it binds to serum proteins, mainly transferrin.² Transferrin is the major iron carrier protein in the circulation. This globulin is responsible for the transportation of iron from its site of absorption to the site of utilization in the cells.³

A number of pathophysiological disorders have been reported in patients with aluminum intoxication. Among them, hypochromic microcytic anemia,⁴ encephalopathy,⁵ Alzheimer's disease,⁶ and vitamin D

resistance osteomalacia⁷ are the most prevalent. In the present investigation, the relationship between aluminum toxicity and some parameters related to bone metabolism has been studied in rats as a model of hemodialysis patients.

MATERIALS AND METHODS

Chemicals

All chemicals were of reagent grade and purchased from Sigma Chemical Company unless otherwise stated.

Animals

Male Wistar rats weighing 250-300 gr (age 2-3 months) were obtained from Medical School of Isfahan University and kept on standard conditions in departmental animal houses.

Aluminum and Bone Metabolism

Treatment

Rats were divided into four groups, two as controls and the other two as experimental animals which were injected with daily intraperitoneal doses of aluminum and/or aluminum in complex with citric acid for 20 or 50 days. On the day of experiments, both control, and aluminum- treated animals were anesthetized and blood samples were withdrawn from their heart directly and allowed to coagulate. Sera were then separated by centrifugation at 1500 rpm and they were either used directly or stored at 4°C.

Biochemistry

Serum calcitonin and parathormone were measured by radioimmunometric technique using commercial kits purchased from DPC (Los Angeles, U.S.A). Serum ALKP activity was assayed by the method of Bessy, et al.⁸ Serum calcium, phosphorous, urea and creatinine were determined by routine laboratory methods.

RESULTS

The acute and chronic effect of aluminum and aluminum citrate on serum bone related parameters was studied.

In order to carry out the present project, two simultaneous protocols were established. In the first protocol, the short term effect (20 days) of aluminum (2 mg/kg) as AlCl₃ with and without citric acid (1:1) on serum calcium, phosphorous, ALKP, PTH and calcitonin concentrations was studied. In the second protocol, the effect of 1 mg Al/kg BW either as AlCl₃ or in complex with citric acid on the same serum parameters was studied.

Citric acid has been well known to accelerate the absorption of aluminum through the gastrointestinal tract by forming a complex with aluminum.⁸

Initially, the effects of both forms of aluminum as AlCl₃ and aluminum in complex with citric acid on renal function was studied by determining serum urea and creatinine concentrations. It was found that administration of either forms of aluminum lead to the elevation of serum creatinine and urea concentrations by 15 and 19 percent respectively, suggesting the disturbances of renal function following aluminum administration (Table I).

The results obtained from the first protocol showed that administration of 2 mg/kg of aluminum either as AlCl₃ or AlCl₃ in complex with citric acid for 20 days elevated serum phosphorous by 15 and 21 percent respectively, whereas serum calcium remained unchanged. Administration of aluminum-citrate (1:1) for 20 days increased serum ALKP concentration by 15

Table I. The effect of aluminum on serum urea and creatinine levels in rats. Each figure indicates the mean \pm SD of five experiments. For the aluminum doses used in the experiments, see text.

| | Urea mg/100 | creatinine mg/100 |
|---------------|----------------|-------------------|
| Control | 30.0 \pm 2.7 | 1.5 \pm 0.22 |
| Aluminum | 33.0 \pm 3.2 | 1.84 \pm 0.20 |
| Alum- Citrate | 36.0 \pm 5.2 | 1.72* \pm 0.23 |

* Statistically significant difference between control and experimental group ($p < 0.05$).

and 29 percent respectively. Serum PTH and calcitonin levels were also studied. It was found that aluminum and/or aluminum- citrate complex markedly reduced serum calcitonin concentration by 42 and 43 percent respectively, whereas PTH levels did not change significantly. The results obtained from the second protocol were approximately comparable with those of protocol number one, suggesting that the effect of aluminum on serum parameters related to bone metabolism is time and dose dependent.

DISCUSSION

It is now well documented that aluminum intoxication causes vitamin- D- resistant osteomalacia in chronic renal failure maintained on hemodialysis.⁹ The data which have been presented here may be able to elucidate the probable mechanism by which the bone disturbances occur. Data in Table I shows that aluminum is a potent toxic agent for the renal function which was shown by the elevation of serum creatinine and urea by 15 and 19 percent respectively. The elevated serum aluminum may accumulate in the bone and cause bone metabolism disturbances.¹⁰ It has been

Table II. The acute and chronic effects of aluminum and aluminum citrate complex on serum Ca, P, ALKP, PTH and calcitonin. Values are mean \pm SD of five separate experiments and expressed in mg/dl for Ca and P concentration. The unit of ALKP is in IU/L. PTH and calcitonin concentrations are expressed in mg/dl.

| Serum parameters | Ca | P | Alk p | PTH | Calcitonin |
|------------------|-------------------|-----------------|-----------------|----------------|---------------|
| Control | A 10.9 \pm 0.73 | 6.8 \pm 0.55 | 49 \pm 4 | 17 \pm 5.6 | 24 \pm 2.9 |
| | B 11.9 \pm 0.60 | 6.6 \pm 0.50 | 50 \pm 3.9 | 17.5 \pm 6.0 | 23 \pm 3.0 |
| Aluminum | A 10.4 \pm 0.33 | 7.8 \pm 0.72 | 56 \pm 1.6 | 18 \pm 6.5 | 14 \pm 7.5* |
| | B 10.6 \pm 0.32 | 7.9 \pm 8.6* | 61 \pm 4.1* | 18 \pm 4.0 | 14 \pm 2.3* |
| Alum- Citrate | A 10.9 \pm 0.41 | 8.3 \pm 0.50* | 62 \pm 2.3* | 18 \pm 3.9 | 14 \pm 4.9* |
| | B 10.9 \pm 0.36 | 8.3 \pm 1.1* | 63.6 \pm 0.5* | 17 \pm 6.7 | 14 \pm 2.3* |

A= rats were given aluminum or aluminum-citrate daily for 20 days.

B= rats were given aluminum or aluminum- citrate daily for 50 days.

* Statistically significant difference between control and experimental group ($P < 0.05$).

reported that aluminum prevents calcification of bone cells following deposition between matrix and calcification front.¹¹ The present data showed that aluminum administration elevated serum phosphorous by 22 percent and alkaline phosphatase concentration by 28 percent respectively (Table II). Observation of Kerr, et al¹² showed that serum aluminum concentration in patients with chronic renal failure maintained on regular hemodialysis was increased from 38.5 ug/l to 50 ug/l after one year of hemodialysis. The PTH level remained unchanged and serum phosphorous was elevated from 2.45 ug/dl to 2.58 ug/dl. Ellis, et al reported that aluminum administration to rats did not change calcium concentrations whereas a significant elevation of serum phosphorous and alkaline phosphatase concentrations were seen.¹³ Our observations were in concordance with their findings. The dose in this report and specific time intervals did not have significant effect on this hormone level (Table II).

Our data also showed that the calcitonin level decreased significantly following aluminum administration (Table II). The observed changes in calcitonin level following aluminum administration indicates that the effect of aluminum on bone metabolism is probably partly mediated by changes in thyroid cell function. However more investigations in this and other laboratories should be carried out to find out the exact mechanism by which the bone disease occurs in patients with chronic renal failure maintained on hemodialysis.

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