The relationship between high maternal aluminum ingestion and anemia-related hematologic changes in rats

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Microcytic, hypochromic anemia in dialysis patients has been associated with aluminum toxicity. Since pregnant women and infants are high-risk groups for iron-deficiency anemia, the purpose of this study was to investigate if high maternal aluminum intake could cause anemia in dams and pups of rats. Eighteen Sprague-Dawley (SD) female weanling rats were arranged in three groups under randomized completely block design (RCBD) experiment design. Control, Low-Al and High-Al groups had 0, 500, 2000 mg Al/kg diet added in the basal diet, respectively, through growing, pregnancy and lactation. Rats were sacrificed after weanling. Results indicated that either body weight gain or feed efficiency was the lowest in High-Al groups dams ($P<0.05$). The body weights were the same in neonates from mothers with various aluminum intakes. However, the higher the maternal aluminum intakes, the lower the average body weight of weanling pups ($P<0.05$). There was a positive correlation between Al intake and serum Al concentration, Al intake and milk Al content of dams ($r = 0.93$ and $r = 0.89$, respectively; $P<0.05$). Average milk and serum aluminum concentrations of dams with high aluminum intake were higher than those in the Control and Low-Al groups. Nevertheless, serum aluminum concentration in pups was not different among the three groups. There was no difference in hematocrit (Hct), hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), total iron binding capacity, or transferrin saturation among dams. On the other hand, the pups in the High-Al group had the highest Hct and Hb per unit body weight compared with the other groups, probably due to smaller litter size.

Introduction

Aluminum toxicity has been associated with microcytic, hypochromic, non-iron deficiency anemia[1,2]. The mechanism of aluminum-induced anemia is still unclear. Although evidence indicated that aluminum inhibited hemoglobin synthesis[3,4], the step in which Al interfered in the hemoglobin synthesis process needs to be studied further. In vitro, growth of hematocytes was retarded by adding Al to the cell culture medium, however, this inhibition was not seen in vivo[3]. It was also suggested that aluminum probably stagged the mobilization and/or transport of iron from storage site.

Anemia is one of the most prevalent health problems in the world. Thirty per cent to 8% of the population in developing and developed countries, respectively, suffer from a certain degree of anemia[5]. The high-risk groups are pregnant women and young children whose anemic conditions are known to be iron deficient.

Although animal studies indicated that the placenta may have a protective effect against Al for the fetus, maternally ingested, Al could partially pass through and influence development of the fetus[6,7]. Aluminum can also affect the growth of pups by entering through maternal milk[8].

Basically, physiological activities, including blood cell formation, are very high during pregnancy, lactation, and child growing periods. Therefore, whether a high maternal intake of aluminum would cause anemia in the mother and the young child is something to be concerned about. In this study, female rats were fed with a high aluminum diet during growing, pregnancy, and lactation to investigate the anemia-related hematological changes, if any, in both dams and pups.

Materials and methods

Twenty-four weanling Sprague-Dawley rats from six litters, one male and three females in each litter, were purchased from the National Defense Medical College Animal Center (Taipei, Taiwan, ROC). Each rat weighed about 40 g. Following the randomized completely block design (RCBD), one of three female rats from the same litter was randomly assigned to the Control, Low-Al, or High-Al groups. Each group had six female rats.

Control group and all male rats were fed with a basal diet, formulated as AIN–76 rat diet[9,10]. Low-Al and High-Al diets were also based on the basal diet, except that 7 g and 28 g of $Al(NO_3)_3 \cdot 9H_2O$ (Hawana, Extra pure reagent, Japan) per Kg diet was used to substitute for the amount of sucrose removed, to make a 500 mg Al, and 2000 mg Al per Kg diet, respectively (Table 1). In order to prevent the formation of insoluble aluminum phosphate causing phosphorus deficiency, 7.6 g per Kg diet of $Ca(H_2PO_3)_2 \cdot H_2O$ was added in each diet to attain a phosphorus content of 0.6%, and a calcium to phosphorus ratio of 1 to 1.06. These values are within the range recommended by NRC for phosphorus content and Ca/P ratio of diets for growing rats[11]. Six samples of each diet were collected for determination of Al and Fe content.

Animals were individually housed in a stainless steel cage, with 12-hour light and 12-hour dark periods,

Table 1. Composition of rat diets.

Group	Control	Low-Al g/kg diet	High-Al
Casein	20.0	20.0	20.0
DL-Methionine	0.3	0.3	0.3
Sucrose	42.4	41.7	39.6
Corn Starch	15.0	15.0	15.0
Cellulose	5.0	5.0	5.0
Corn Oil	5.0	5.0	5.0
Choline Bitartrate	0.2	0.2	0.2
Mineral Mix[1]	3.5	3.5	3.5
Vitamin Mix[2]	1.0	1.0	1.0
$Ca(H_2PO_3)_2H_2O$	7.6	7.6	7.6
$Al(NO_3)_39H_2O$	–	0.7	2.8

[1]AIN mineral mixture 76, ICN Pharmaceuticals, USA.
[2]AIN vitamin mixture 76, ICN Pharmaceuticals, USA.

20–22°C and 60–70% relative humidity. Recorded amounts of food and deionized water were provided ad libitum. The body weight of each animal was obtained once a week.

One male was mated to three female rats from the same litter after five weeks of feeding. At that time, male and female animals weighed about 230 g and 200 g, respectively. Because the male and female rats were in the same cage during mating, treatments were temporarily disrupted and resumed after the female rat was pregnant. After 21 days of pregnancy, females started to deliver. Litter size was determined and half of the neonates were killed to have their body weight and organ weight measured. The remaining half of the rats were breast-fed by dams. Milk was collected on day 14 of lactation to determine the Al and Fe concentrations. Pups were weaned at day 21 of lactation. Then both dams and pups were killed after being anesthetized by pentobarbitol injection. Whole blood and serum of dams and pups were collected for hematorit (Hct), hemoglobin (Hb), serum Fe, transferrin saturation, and serum aluminum measurements. Body weight and organ weight of the rats were also measured.

For Hct determination, whole blood was collected into a Hct capillary tube with anticoagulant to ⅔ full, the tube was turned upside down and one end was sealed with glue. The tubes were arranged in a centrifugal disk with 10 500 × g, for 10 minutes of centrifugation (Centrifuge; Hermle Z320, Germany). Each sample was tested twice. Hb concentration was determined by the cyanomethemoglobin method[11]. Serum and milk iron was analyzed by spectrophotometry[12] after adding an ascorbic acid-containing acid buffer and a color developing reagent (ferrozine) into the samples. Total iron binding capacity (TIBC) was measured by modified Du's method[12]. Transferrin saturation was calculated from the values of serum Fe divided by TIBC and then multiplied by 100%. Aluminum content of all samples was determined by using an Atomic Absorption Spectrophotometer (AAS, 902BC, GBC, Australia) with graphite furnace (System 2000, GBC, Australia) and Autosampler (Programmable Auto Loader; PAL 2000, Australia). The instrument was adjusted at a wavelength of 309 nm, a slit of 0.5 nm, a Hollow cathode Al lamp, a lamp current of 10.0 mA, integrate time 1 sec, double beam and D2-background correction were used. Various amounts of modifier, which was composed of 0.1% HNO_3 (E. Merck, Darmstadt) 1.4 g/l Mg $(NO_3)_2$. $6H_2O$ (E. Merck, Darmstadt) and 0.2% Triton X-100 (E. Merck, Darmstadt) were added to the samples.

One way ANOVA (analysis of variance) was done for all measurements of the three groups at $\alpha = 0.05$ level of significance, then Duncan's multiple range test was used to test the significance of difference ($P<0.05$). Linear regression was used to evaluate the correlation among variables.

Results

Results indicated that average water intake of dams in the High-Al group (33.2±6.0 ml/day) was significantly higher ($P<0.05$) than the Low-Al group and Control group (Table 2). Average daily water intake per kg body weight in the High-Al group was also the highest among the three groups ($P<0.05$). Average food intake in the High-Al group was lower ($P<0.05$) than the Low-Al group, but there was no difference between the High-Al group and Control animals (17.6 g/day). However, average food intake per kg body weight per day of rats in the High-Al group was higher than the other two groups ($P<0.05$).

Al concentration in the three diets were 27.9, 586.8 and 2413.5 mg/kg, respectively. Considering body weight and daily food intake, mean daily aluminum intake per kg body weight were calculated as 2.16, 43.13, and 231.68 mg/kg b. wt with a ratio of about 1:20:100. The differences between the three groups were significant ($P<0.05$). There was a positive correlation between Al intake and water intake ($r = 0.92$, $P<0.05$), also water intake and food intake ($r = 0.85$, $P<0.05$). Average daily iron intake per kg body weight of the three groups was the same (see Table 2).

Table 2. Average water and food intakes of rats fed various levels of aluminum nitrate[1,2,3].

Group	Control	Low-Al	High-Al
Water			
ml/day	22.5±0.4[a]	23.6±2.1[a]	33.2±6.0[b]
ml/kg b.wt/day	90.7±23.1[a]	98.4±19.7[a]	188.6±16.9[b]
Feed			
g/day	17.6±0.4[a,b]	17.7±0.9[a]	16.7±1.0[b]
g/kg b.wt	77.4±12.4[a]	73.5±9.3[a]	96.0±1.0[b]
Al mg/kg b.wt/day	2.16±0.34[a]	43.13±5.45[b]	231.68±28.81[c]
Al intake ratio	1	19.96	107.25
Fe mg/kg b.wt	4.21±0.48	3.92±0.50	4.60±0.57

[1] Values are Mean±SD (n=6).
[2] Values in the same row with different superscripts are significantly different ($P<0.05$).
[3] Aluminum concentrations in Control, Low-Al and High-Al diets are 27.93±7.65, 586.85±59.43 and 2413.48±395.83 mg/kg diet, respectively.

Mean body weight gain of dams in the High-Al group was lower than the other two groups ($P<0.05$), although there was no difference at the beginning (Table 3). Meanwhile, the average feed efficiency in the High-Al group animals was the lowest ($P<0.05$) among the three groups. Compared with the Low-Al group, the High-Al group had a smaller litter size ($P<0.05$), but the average body weight of neonates, was the same among the three groups. The average body weight of weanling rats seemed to decrease with an increasing Al content in the dam's diet ($P<0.05$). Examining organ to body weight

Table 3. Mean body weight gain, feed efficiency and litter size for dams and pups[1,2].

Group	Control	Low-Al	High-Al
Dam	(n=6)	(n=6)	(n=6)
B.wt gain (g)	187.38±21.83[a]	201.66±28.23[a]	131.72±23.94[b]
Feed efficiency[3]	0.14±0.02[a]	0.15±0.02$_a$	0.10±0.02[b]
Pup			
Litter size	10.3±3.4[a,b]	11.0±3.57[a]	7.5±2.6[b]
Neonate's b.wt	5.96±0.41	5.89±0.89	5.86±0.93
(g)	(n=28)	(n=32)	(n=23)
Weanling's b.wt	40.51±5.81[a]	35.16±9.10[b]	31.84±5.60[c]
(g)	(n=32)	(n=34)	(n=21)

[1] Values are Mean±SD.
[2] Values in the same row with different superscripts are significantly different ($P<0.05$).
[c] Feed efficiency = b.wt gain/total intake.

Table 4. Relative organ weight of dams and pups[1,2].

Group	Control	Low-Al g/100g b.wt	High-Al
Dam	(n=6)	(n=6)	(n=6)
Liver	4.28±0.84	4.03±0.77	3.45±0.28
Spleen	0.21±0.03	0.20±0.03	0.22±0.03
Kidney	0.91±0.19	0.88±0.07	1.00±0.20
Pup			
Neonate	(n=28)	(n=32)	(n=23)
Liver	4.87±0.05	5.02±0.77	4.81±0.76
Spleen	0.20±0.04	0.19±0.05	0.20±0.06
Kidney	1.19±0.13	1.19±0.20	1.20±0.19
Weanling rat	(n=32)	(n=34)	(n=21)
Liver	3.72±0.36	3.62±0.28	3.68±0.60
Spleen	0.39±0.08	0.39±0.08	0.38±0.05
Kidney	1.34±0.11	1.37±0.13	1.40±0.15

[1] Values are Mean±SD.
[2] There is no statistical difference among values in same parameter ($P>0.05$).

ratio (including liver, spleen and kidney) of dams and pups (Table 4), revealed that values were the same among the three groups.

Serum Al and Fe were checked in both dams and pups. A significantly higher serum Al was found in the High-Al group dams with a mean value of 36.61 μg/1) but not in pups (Table 5) Meanwhile, average aluminum content of milk in the High-Al group (136.22 μg/1) was the highest ($P<0.05$) among the three groups. In addition, the ratio of Al content in milk of the three groups was about 1:1:2 (see Table 5). There was no difference of serum iron both in dams and pups among the three groups (see Table 5). Milk iron content was also similar in the three groups.

Table 5. Aluminum and iron contents of serum and milk in rats fed various amount of aluminum[1,2].

Group	Control	Low-Al	High-Al
Serum Al		μg/l	
Dam (μg/l)	12.74±1.68[a]	10.62±3.17[a]	36.61±5.68[b]
	(n=6)	(n=6)	(n=6)
Pup (μg/l)	16.98±11.96	18.53±9.60	18.42±9.02
	(n=32)	(n=34)	(n=21)
Milk Al			
Dam (μg/l)	64.12±13.56[a]	65.74±14.86[a]	136.22±26.54[b]
	(n=6)	(n=6)	(n=6)
Al Ratio	1	1.02	2.12
Serum Fe			
Dam (mg/L)	2.73±0.41	2.34=0.55	3.32±8.81
	(n=6)	(n=6)	(n=6)
Pup (mg/L)	1.33±1.42	1.25±1.15	1.05±1.32
	(n=32)	(n=34)	(n=21)
Milk Fe			
Fe (mg/L)	1.93±2.08	1.05±0.65	2.85±1.19

[1] Values are Mean±SD.
[2] Values in the same row with different superscripts are significantly different ($P<0.05$).

There were no differences in any hematological measurements among dams, including Hct, Hb, MCHC (mean corpuscular hemoglobin contration), TIBC and transferrin saturation (Table 6). On the other hand, the lowest Hct ($P<0.05$) was found in weanling pups of the Low-Al group with a mean value of 16.85%. In addition, Hb was lower in the Low-Al group pups (78.3 g/l) than in the High-Al group pups (84.3 g/l). However, if the values were adjusted with body weight, the highest values of Hct and Hb were shown in the High-Al group (0.57%/g b. wt (= body weight) and 0.26 g/dl/g b. wt, respectively). All pups had similar MCHC, TIBC and transferrin saturation (see Table 6).

Table 6. Hematological parameters of dams and pups at weanling[1,2].

Group	Control	Low-Al	High-Al
Dam	(n=6)	(n=6)	(n=6)
Hct (%)	32.53±2.70	33.70±4.95	34.35±2.40
Hb (g/dl)	15.38±0.41	14.67±0.60	15.62±1.31
MCHC[3]	47±1	44±2	45±4
TIBC (mg/dl)[4]	0.43±0.08	0.36±0.05	0.42±0.06
Tf saturation(%)[5]	64.93±15.10	63.35±12.79	78.15±16.89
Pup	(n=32)	(n=34)	(n=21)
Hct (%)	18.42±2.95[a]	16.85±2.11[b]	18.19±2.25[a]
(%/g b.wt)	0.45±0.07[a]	0.48±0.06[a]	0.57±0.07[b]
Hb (g/dl)	8.29±1.18[a,b]	7.83±0.92[a]	8.43±1.00[b]
(g/dl/g b.wt)	0.20±0.01[a]	0.22±0.03[a]	0.26±0.03[b]
Serum Fe (mg/dl)	0.13±0.14	0.12±0.11	0.10±0.13
TIBC (mg/dl)[4]	0.88±0.19	0.93±0.21	1.03±0.26
Tf saturation(%)[5]	16.36±18.90	13.85±11.88	10.81±17.06

[1] Values are Mean±SD.
[2] Values in the same row with different superscripts are significantly different ($P<0.05$).
[3] MCHC = Hb (g/dl) × 100/Hct (%).
[4] TIBC: Total Iron Binding Capacity.
[5] Tf saturation: Transferrin saturation = serum iron/total iron binding capacity × 100%.

Discussion

Llobet et al.[13] demonstrated that 14 days LD_{50} for oral intake of $Al(NO_3)_3$ was 3632 mg/kg b. wt which contained 261 mg Al/kg b. wt. In our study, High-Al dams consumed 231.7±28.8 mg/kg b. wt, which included 2000 ppm $Al(NO_3)_3$ added in the diet and Al from other ingredients, approximately 88% of $Al(NO_3)_3$ LD_{50}. However, all animals survived through the experimental period (growing, pregnancy and lactation). A possible explanation was that not all of Al in diets was in the form of $Al(NO_3)_3$. In addition, the feeding method, such as same dose in one feeding or several feedings, might play a role in Al effects.

From the results of higher food intake, there was a lower body weight gain and lower feed efficiency in High-Al dams. The negative correlation between Al intake and body weight gain and serum Al and body weight gain indicated that high aluminum ingestion might influence bioavailability of other nutrients and cause growth retardation in rats. Similar results have been reported by another study in which pregnant dams were fed $Al(NO_3)_3$ for three weeks[14].

Although High-Al dams had the lowest body weight gain, the neonates in the High-Al group were not smaller than other groups, and this could probably be due to the smaller litter size of the High-Al group. It seemed quite reasonable that in the case of a maternal nutritional deficiency in multi-embryo species, a reduction of off-

spring number might be the result of trying to maintain a normal weight for each fetus.

In our study, it was shown that body weight of pups decreased as aluminum ingestion by dams increased during lactation. This adverse effect of Al might be caused by quality and/or quantity of milk produced by dams, since body weight of dams was also influenced by Al ingestion. Nevertheless, Al content in dams' diets had a ratio of 1:20:100, and Al content in milk of the three groups had a ratio of 1:1:2. Therefore, this low body weight gain in the pups seemed to be due to the quantity of milk produced by the high aluminum ingestion of dams. Yokel[15] had demonstrated a decrease of milk production in one rabbit by subcutaneous injection of Al. However, there was no data on the amount of milk produced by dams in our study. According to the result of a human study, Greger & Baier[16] suggested that Al might bind with phosphate in the gastrointestinal tract to reduce phosphate absorption. Nevertheless, phosphorus depletion does not appear to be the case in our study, since the Al content in milk was in parts per billion which was much lower than the phosphorus content reported in mg/l. On the other hand, Domingo and associates[17,18] demonstrated that the inhibition of growth by Al was not so obvious while the pups were getting older. Another study which supported this finding reported that pups who were born from dams administered with Al during pregnancy had low body weight, which increased to values similar to the control group after nine days during which Al ingestion of dams was stopped[19].

Although average body weight was lower, each organ to body weight ratio in the High-Al dams or weanling rats was the same as the other two groups. A similar result was reported in Domingo's studies in which weanling female rats were fed 250 mg/kg b. wt daily for 100 days without mating[17] and weanling pups were from dams tube-fed $Al(NO_3)_3$ for two weeks prior to mating[20]. Organ to body weight ratios of neonates were also not influenced by the maternal Al ingestion in our study. Domingo[21] had the same results in newborn of dams with daily ingestion of 266 mg Al/kg b. wt from $Al(OH)_3$.

In our study, Hct, Hb, MCHC, serum Fe, TIBC and transferrin saturation were not affected by the ingestion of Al in dams. Similar results were reported in weanling female rats fed $Al(NO_3)_3$ with the amount of LD_{50} for 100 days[17]. On the contrary, intra-peritoneal injection of 1 mg Al per day for three weeks caused a significant reduction of Mean Corpuscular Volume (MCV) in rats with normal renal function. In addition, Hct and Hb values were lowered at week 4 and 6 of the experiment[22].

In weanling pups in the Low-Al group, the lower Hct and/or Hb values in comparison to the other groups, seemed to be due to the significantly larger litter size. This could be further proved by the highest values of Hct and Hb per unit body weight shown in the High-Al group pups which had the lowest litter size among the three groups.

The lack of toxicity of aluminum ingestion on hemopoiesis in rats is probably due to the low absorption rate of aluminum in animals with normal renal function. Greger & Power[23] reported a 0.011–0.036 of aluminum absorption in weanling SD rats fed 1–3 g Al as aluminum hydroxide per kilogram diet. They used a modified method to compare tissue accumulation of aluminum in relation to dose in animals fed aluminum and in animals matched for age and weight and injected with aluminum. In vitro, hemopoiesis was inhibited in medium contained 185–3704 μM aluminum[3] which was much higher than the aluminum content in the serum of High-Al group dams and pups, 36.61 and 18.42 ug/1, respectively, in our study. Therefore, it is concluded that maternal intake of Al up to 2 mg/kg from $Al(NO_3)_3$ may not affect dams and pups hematologically. However, growth of rats would be influenced by a high intake of aluminum.

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摘　要

本實驗之目的在探討母鼠攝食鋁是否造成母鼠及其子代貧血。剛離乳之雌性大白鼠以逢機完全區集設計分為控制組，低鋁組與高鋁組，餵食添加不同鋁量(0, 500, 2000 mg/kg diet)之飲食，經成長，懷孕，哺乳期，哺乳至第十四天擠取鼠奶，幼鼠斷奶時犧牲動物．結果顯示，高鋁組母鼠之體重增加與飼料效率均較其他二組低($P<0.05$)，其血清，乳汁鋁含量均顯著高於控制及低鋁組($P<0.05$)。母鼠鋁的攝取量與血清，乳汁鋁含量成正相關($r=0.93$，$r=0.89$；$P<0.05$)．小鼠離乳時，體重有隨母鼠攝鋁量增加而較輕之現象($P<0.05$)，血清鋁在小鼠三組間無差異．母鼠之血比容，血色素，血清鐵及血清輸鐵蛋白飽和度三組間均無差異．但高鋁組小鼠之單位體重血色素和血比容較其它兩組高，可能是因胎數較少之原故．