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Aluminum loading in children with chronic renal failure

AILEEN B. SEDMAN, NANCY L. MILLER, BRADLEY A. WARADY, GARY M. LUM, and ALLEN C. ALFREY

University of Colorado Health Sciences Center and Veterans Administration Medical Center, Denver, Colorado

Aluminum loading in children with chronic renal failure. Plasma aluminum levels were measured in 17 children with chronic renal failure who were receiving aluminum containing antacids for the control of hyperphosphatemia. Seven children were on hemodialysis, five on peritoneal dialysis, and five were awaiting dialysis with creatinine clearances between 10 to 20 cc/min/1.73 m^2. Plasma aluminum levels correlated directly with oral aluminum dosage; extremely high levels were documented in small, nondialyzed children. Bone aluminum levels were measured in four children with high plasma levels and confirmed significant aluminum loading. Other factors such as the level of aluminum in dialysate and tap water were measured and were not contributory. All patients with plasma aluminum levels greater than 100 μg/liter had signs of aluminum toxicity and were receiving greater than 75 mg/kg/day of elemental aluminum orally. We concluded that children who require greater than 30 mg/kg/day of elemental aluminum to control hyperphosphatemia should have plasma aluminum levels monitored and/or be considered for other forms of therapy including more restricted diets and earlier or more aggressive dialysis.

Surcharge aluminique chez des enfants en insuffisance rénale chronique. Les concentrations plasmatiques d'aluminium ont été déterminées chez 17 enfants en insuffisance rénale chronique recevant des antiacides contenant de l'aluminium pour contrôler leur hyperphosphatémie. Sept enfants étaient en hémodialyse, cinq en dialyse péritonéale et cinq étaient en attente de dialyse avec des clearances de la créatinine entre 10 à 20 cc/min/1.73 m^2. Les niveaux plasmatiques d'aluminium étaient directement corrélés à la dose orale d'aluminium; des niveaux extrêmement élevés ont été documentés chez de petits enfants non dialysés. Les niveaux d'aluminium osseux ont été mesurés chez quatre enfants avec des niveaux plasmatiques élevés et confirmant une surcharge aluminique significative. D'autres facteurs comme le niveau d'aluminium dans le dialysat et l'eau du robinet ont été mesurés mais n'étaient pas contributifs. Tous les malades dont l'aluminium plasmatique dépassait 100 μg/litre avaient des signes de toxicité aluminique et recevaient >75 mg/kg/jour d'aluminium-élément oralement. Nous avons conclu que les enfants nécessitant >30 mg/kg/jour d'aluminium-élément pour contrôler leur hyperphosphatémie devraient avoir leur niveau plasmatique d'aluminium surveillé, et/ou devraient être candidats à d'autres formes de traitement notamment des régimes plus restreints et une dialyse plus précoce ou plus agressive.

Epidemiologic and animal data have implicated aluminum as one causative factor for dialysis dementia and osteomalacic osteodystrophy [1–4]. Previous work has demonstrated a high correlation between aluminum loading and the dialysate aluminum in hemodialysis patients [3]. There is less definite correlation with oral intake of aluminum, although there are substantial data to indicate that oral loading can take place [5]. Previous reports have suggested aluminum toxicity in children, but increased plasma and tissue levels have only recently been documented [6–8].

The extremely high rate of developmental delay and bone disease in medically managed children with chronic renal failure [9] has prompted us to explore further the issue of aluminum toxicity in childhood secondary to oral exposure.

Methods

Blood samples were collected by venipuncture. Red cells and plasma were separated by centrifuge immediately after collection, and plasma was placed in plastic test tubes to avoid contamination. Samples were then frozen until the day the analysis was performed. Plasma levels were determined in duplicate by methods previously described using a flameless atomic absorption spectrophotometer (model 305B, Perkin Elmer, Norwalk, Connecticut) [5]. Bone biopsy was performed with a Jamshedi needle sampling of the iliac crest. Bone aluminum was measured by flameless atomic absorption using methods previously described [10].

The patients in our study were 0.5 to 18 years of age, either enrolled in our dialysis program or followed in our renal clinic, with the exception of patients 16 and 17 whose samples were sent to our laboratory from other centers after the children developed bone disease and encephalopathy. All children had received aluminum-containing phosphate binders as $Al(OH)_3$ or $Al_2(CO_3)_3$ to control serum phosphorus between 4.5 to 6.5 mg/dl. Two children in our program with high plasma levels of aluminum subsequently had bone biopsies and then an analysis of aluminum was made from their peritoneal dialysate. Aluminum clearance was measured in four other children in the peritoneal dialysis group, but dialysate levels were so low that they were felt to be unreliable. Aluminum clearance by hemodialysis has been previously described [11, 12] and was not measured in this population.

Results

Plasma aluminum, bone aluminum, patient age and weight, average aluminum dose in milligrams per kilogram, and duration of aluminum therapy are reported in Table 1. It should be noted that patient 13 is reported when he was nondialyzed and then at two different stages of dialysis when his dose of phosphate binders was changed. Duration of therapy for children on dialysis was calculated only during the time the children were

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Table 1. Patient data

	Patient no.	Plasma level[a] μg/liter	Bone level[b] mg/kg	Age years	Weight kg	Dose mg/kg/day	Duration therapy months
Hemodialysis	1	26	—	18	41	20	33
	2	48	—	13	18	48	44
	3	13	—	15	60	58	7
	4	10	—	10	23	45	3
	5	72	—	10	20	52	6
	6	26	—	18	42	13	34
	7	42	—	14	25	84	60
Peritoneal	8	62	—	6	14	39	9
	9	29	—	10	23	47	6
	10	58	—	11	21	82	12
	11	68	—	11	20	29	36
	12	133	82	3.5	8.6	210	15
	13	177	—	1.6	9	93	21
No dialysis	14	65	—	0.5	6	34	5
	13[c]	363	85	1.1	7.6	133	15
	13[c]	312	—	1.3	8	105	17
	15	98	—	12	30	29	30
	16[d]	334	156	3	—	108	25
	17[e]	124	226	3	—	—	7

[a] The plasma level in normal subjects is less than 10 μg/liters (5).
[b] The bone level in normal subjects is less than 3.3 mg/kg (14).
[c] These values represent the same child at various stages of therapy.
[d] Analysis on this child was done at the University of Colorado Health Sciences Center laboratory; the child was from another institution [8].
[e] Analysis on this child was done at the University of Colorado Health Sciences Center laboratory; the child was from another institution (unreported).

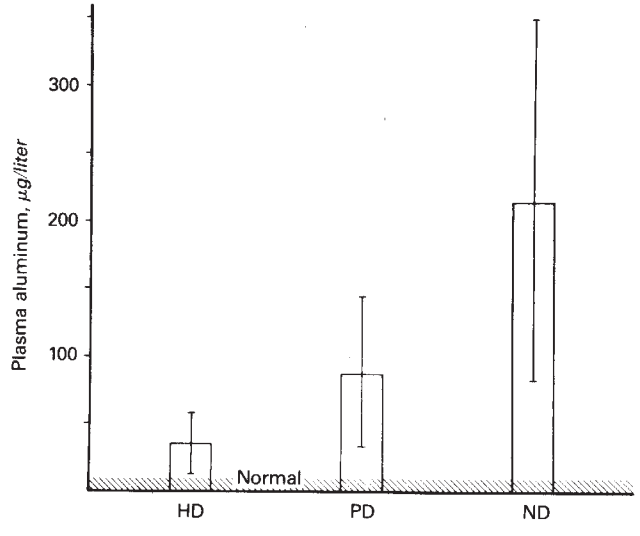

Fig. 1. *Plasma aluminum levels expressed as the mean ± 1 SD in hemodialysis patients* (HD), *peritoneal dialysis patients* (PD), *and patients in chronic renal failure not on dialysis* (ND).

actually dialyzed; records were too incomplete to assess their pre-dialysis therapy. Actual duration of therapy is reported in five nondialyzed children.

All children who received aluminum-containing phosphate binders exhibited higher than normal (N = <10 μg/liter) serum aluminum levels (Fig. 1, 2 $P < 0.005$). The mean level in the hemodialysis group (HD) was 33.9 ± 21.8 μg/liter, in the peritoneal group (PD) 87.8 ± 55 μg/liter, and in the nondialyzed (ND) group 216 ± 134 μg/liter (mean ± 1 SD).

Table 2. Summary of patient data

Patient group	N	Age	Al dose mg/kg/day	Plasma Al μg/liter
HD	7	14 ± 3.3	42.4 ± 25	33.9 ± 21.8
PD	6	8.3 ± 3.3	81.4 ± 79.6	87 ± 55.5
ND	5	5.5 ± 6.0	77.3 ± 50	216 ± 134

Abbreviations: HD, hemodialysis; PD, peritoneal hemodialysis; ND, non-dialyzed.

Patients 12, 13, 16, and 17 were all children diagnosed with renal failure as infants; phosphate binders were used early in their treatment. They exhibited extremely high Al levels compared to normal subjects (Table 1). In fact, several had the highest serum levels ever reported in individuals who had been exposed to oral rather than parenteral aluminum. As shown in Table 2, the average age of nondialyzed patients was younger than those on HD or PD. Four children displayed a clinical syndrome suggestive of aluminum toxicity. Patient 12 had severe growth failure, osteopenia with fractures, and mild developmental delay. Patient 13 had growth failure, osteopenia with an intermittent failure to walk and, although considered to be grossly neurologically normal, was delayed developmentally compared to a non-identical, same-sex twin. Patient 16 (previously reported by Griswold [8]) had growth delay, osteomalacia, and severe encephalopathy including myoclonic seizures with a loss of speech. Patient 17 was a child from another institution with prune-belly syndrome who was never dialyzed. At 2 years of age he had a clearance of 15 ml/min/1.73 m^2 with severe failure to thrive, anemia, and rickets. At that time he was started on aluminum-containing phosphate binders. At 3 years of age he developed seizures refractory to therapy, and aluminum levels were documented by our laboratory to be high (reported in Table 1) in both plasma and bone. The child was subsequently institutionalized without change in therapy. He died at age 6 with evidence of severe encephalopathy and osteomalacia and high tissue and plasma aluminum levels measured by another laboratory.

The direct correlation between elemental aluminum dose and plasma aluminum levels ($r = 0.600$, $P < 0.01$) is expressed in Figure 2.

Patients 12 and 13 had dialysate Al measured after being on chronic ambulatory peritoneal dialysis for at least 6 weeks. With a plasma level of 133 μg/liter, patient 12's dialysate level was 42 μg/liter; patient 13 had plasma of 177 μg/liter with a dialysate level of 45 μg/liter. The aluminum level on infused dialysate was 2 μg/liter.

Discussion

Aluminum is widespread in nature making up approximately 8% of the earth's crust. Lungs, skin, and gastrointestinal tract basically exclude the largest amount of environmental aluminum [13], and the small amounts that are absorbed are excreted in individuals with normal glomerular filtration rate (GFR). Patients with renal failure, however, have been shown previously to accumulate large amounts of aluminum in tissues including spleen, liver, brain, and bone [3]. Good epidemiologic correlation has demonstrated that this abnormal accumu-

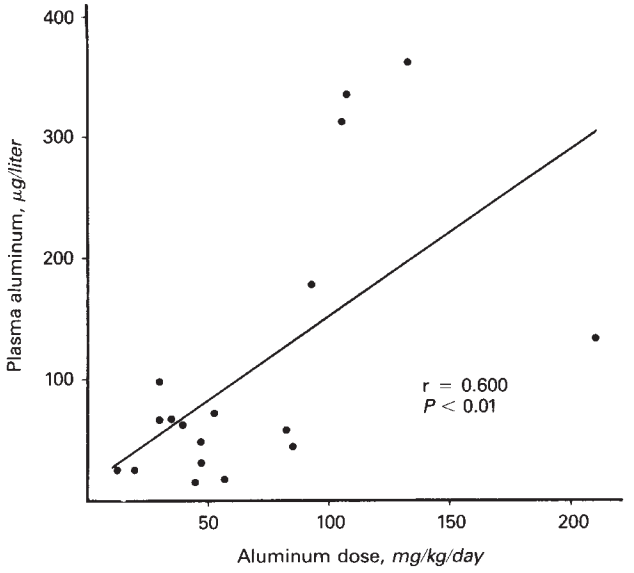

Fig. 2. *Elemental aluminum dose versus plasma aluminum of patients including those on hemodialysis, peritoneal dialysis, and not on dialysis.*

lation causes encephalopathy and vitamin D-resistant osteomalacia [1–4]. The highest levels of tissue accumulation occurred when patients were directly exposed to dialysate contaminated with aluminum. In fact, a severe form of dialysis encephalopathy leading to rapid demise has virtually disappeared from dialysis units where aluminum levels in dialysate have been strictly controlled [14]. The relationship of oral aluminum intake and tissue loading and toxicity has not been as clearly defined, and there is little evidence that oral loading causes very high levels of plasma and tissue aluminum in adults with the frequency that is seen in the children we studied. Studies in children documenting aluminum levels correlated with the dose of oral intake have also been limited, although isolated reports have noted children with encephalopathic symptoms seemingly related to high oral aluminum intake [6, 7].

Our study shows a direct correlation between oral elemental aluminum dose and plasma levels. However, since aluminum is highly tissue-bound, plasma aluminum levels cannot be assumed to directly reflect the amount of tissue loading. High plasma levels are compatible with high bone levels, but individuals with similar plasma levels can have markedly different bone levels (see patients 12 and 17, 16 and 13, Table 1). Tissue levels are most likely related to multiple factors including the level of GFR, duration of therapy, total dose of aluminum, and tissue turnover rate.

The patients who appear to be at most risk for aluminum toxicity are children on maximum binder therapy to control serum phosphorus before dialysis is begun, suggesting that management should include more aggressive limitation of phosphate intake with low phosphorus formula and/or essential amino acid supplements so that aluminum-containing phosphate binders are not as necessary to prevent hyperphosphatemia. We now use oral calcium carbonate as our initial phosphate binder and only utilize aluminum when calcium carbonate is not tolerated either secondary to hypercalcemia or prohibitive volume of antacid. Alternative phosphate binders consisting of heteropolyuronic acid have recently been clinically tested in Europe and appear to be safe and efficacious on a limited basis [15]. They are not yet available in the United States. Earlier dialysis may be helpful especially with low magnesium-containing dialysate to allow use of magnesium-containing phosphate binders [16]. Peritoneal clearance of aluminum without chelation in our patients is moderate, reflecting that aluminum is highly tissue- and protein-bound. Further studies are needed to define the nature of the protein binding.

Our study suggests that the very high levels of aluminum seen in nondialyzed children are directly related to the large amounts of binder required to control serum phosphorus. All patients with plasma aluminum levels greater than 100 μg/liter were receiving greater than 75 mg/kg/day of elemental aluminum and showed signs of toxicity. In comparison to adults who usually consume less than 30 mg/kg/day, this represents an extremely large dose of aluminum and probably accounts for the toxicity noted in small children. In view of this, it seems reasonable to recommend that if children require more than 30 mg/kg/day of elemental aluminum, they have aluminum levels monitored to document that plasma levels are not reaching a range associated with toxicity and/or that they be considered for other methods of management of hyperphosphatemia apart from aluminum-containing phosphate binders.

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Reprint requests to Dr. A. B. Sedman, Pediatric Renal Department, Box 54, Room C1078 Outpatient, University Hospital, 1405 E. Ann, Ann Arbor, Michigan 48109, USA

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