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EVIDENCE OF ALUMINUM LOADING IN INFANTS RECEIVING INTRAVENOUS THERAPY

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Abstract To investigate the possibility that premature infants may be vulnerable to aluminum toxicity acquired through intravenous feeding, we prospectively studied plasma and urinary aluminum concentrations in 18 premature infants receiving intravenous therapy and in 8 term infants receiving no intravenous therapy. We also measured bone aluminum concentrations in autopsy specimens from 23 infants, including 6 who had received at least three weeks of intravenous therapy.

Premature infants who received intravenous therapy had high plasma and urinary aluminum concentrations, as compared with normal controls: plasma aluminum, 36.78±45.30 vs. 5.17±3.1 μg per liter (mean ±S.D., P<0.0001); urinary aluminum:creatinine ratio, 5.4±4.6 vs. 0.64±0.75 (P<0.01). The bone aluminum concentration was 10 times higher in infants who had received at least three weeks of intravenous therapy than in those who had received limited intravenous therapy: 20.16±13.4 vs. 1.98±1.44 mg per kilogram of dry weight (P<0.0001). Creatinine clearances corrected for weight did not reach expected adult values until 34 weeks of gestation. Many commonly used intravenous solutions are found to be highly contaminated with aluminum.

We conclude that infants receiving intravenous therapy have aluminum loading, which is reflected in increased urinary excretion and elevated concentrations in plasma and bone. Such infants may be at high risk for aluminum intoxication secondary to increased parenteral exposure and poor renal clearance. (N Engl J Med 1985; 312: 1337-43.)

ALTHOUGH osteopenia in premature infants has been well documented, the cause of this complication remains to be determined.[1-5] It appears to be directly related to parenteral therapy, since bone-accretion rates have been found to return to normal after infants were given enteral feedings supplemented with calcium, phosphorus, and vitamin D. In contrast, infants who could not tolerate enteral feeding had progressive osteopenia and fractures, which were resistant to standard therapy.[1,5] This suggests that some substance either deleted from or given with parenteral therapy may be responsible for premature osteopenia. Since aluminum has been implicated in the pathogenesis of vitamin D–resistant osteomalacia in human beings and animals, we elected to study this element in premature infants.

Aluminum toxicity in human beings has been described in patients receiving hemodialysis; severe dementia developed, and the patients died as a result of excessive exposure to aluminum in their dialysate and lack of normal renal excretion.[6] Subsequently, it was realized that these patients also had fracturing osteomalacia.[7] Another indication of the skeletal toxicity of aluminum was the demonstration of fracturing osteomalacia in animals by parenteral administration of aluminum.[8,9]

After standards for acceptable concentrations of aluminum in dialysate had been established and dialysis units throughout the world began monitoring the amount of aluminum in their water, the incidence of dementia and fracturing bone disease dropped dramatically.[10] In subsequent years, a more insidious form of bone disease has been described, which is secondary to excessive exposure to oral aluminum.[11-13] The effects are especially devastating in young children with compromised renal function.[12,13] Other studies have provided further evidence that parenteral nutrition solutions contaminated with aluminum cause loading and possibly even bone disease in adults with normal renal function.[14,15] No studies concerning aluminum loading have thus far been carried out in premature infants who are known to have a high incidence of osteopenia.

We have found high concentrations of aluminum in bone, urine, and plasma from infants receiving intravenous therapy. It seems possible that aluminum loading may be a factor in the bone disease seen in very ill neonates who have reduced renal function and have received long-term parenteral therapy with aluminum-contaminated fluids. It is not known whether

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relatively short-term high concentrations of aluminum in plasma and bone in premature infants can reproduce the toxicity that chronic loading causes in older children and adults with chronic renal failure.

Methods

We measured aluminum concentrations in plasma, urine, or bone in five groups of patients. Group I included 18 premature infants (≤37 weeks of gestation) who required admission to the intensive care unit and intravenous therapy. Plasma and urinary aluminum concentrations were measured in these 18 infants on two different occasions approximately three weeks apart; 9 were studied on the first day of life and three weeks later, and 9 were studied at a random time (11 to 42 days of age) and three weeks later. Urinary and serum creatinine levels were measured in infants who were more than one week old at the time of the study. Creatinine was not measured in infants less than one week of age, because the concentrations were thought to be a reflection of the mother's creatinine and not that of the infant. In 13 infants complete 24-hour samples were collected at the three-week study; in the remainder of the infants 24-hour collections were incomplete and thus could not be used for calculation of clearances.

Group II included eight term infants who did not require intravenous therapy (normal controls). In four of these infants plasma and urinary aluminum concentrations were measured at one day and three weeks of age, and in the other four, aluminum concentrations were measured at one visit. Aluminum was also measured in 35 umbilical-cord plasma samples, to establish a normal base line; these values are reported with normal control measurements.

To estimate the amount of aluminum being given to and retained by infants who were receiving only intravenous therapy, we studied a third group of five infants (Group III) who had been receiving intravenous therapy for at least two weeks. Intake and excretion of aluminum in the urine were measured for a period of two or three days.

Clinical data on the three groups of infants are shown in Tables 1, 2, and 3. Parents were required to sign a standard consent form before the infants were enrolled in the prospective study.

Autopsy specimens were collected from 23 infants (age range, 0 to 7 months) and divided into two groups. Seventeen of the infants (Group IV) did not receive prolonged parenteral therapy because they died in the emergency or delivery room or within one week of hospitalization. Representative diagnoses at the time of death included the sudden infant death syndrome, severe prematurity, and congenital cardiac defect. The other six infants (Group V) had received at least three weeks (mean ±S.D., 9.6±5.2) of parenteral nutrition before death (considered long-term parenteral nutrition). All these infants were under 37 weeks of gestation and required parenteral nutrition secondary to necrotizing enterocolitis, congenital malformation of the gastrointestinal tract, or severe feeding intolerance. One member of this group was a premature infant who had been discharged from the hospital at four months of age but died in the emergency room at six months, with a diagnosis of sudden infant death syndrome. The other five infants were inpatients at the time of death.

Plasma and urine samples were collected by clinical research nurses or technicians trained in study collection techniques. To avoid exogenous contamination of plasma samples until completion of the analysis, the skin was carefully cleansed with deionized water, and samples were collected in unaltered plastic containers and frozen in plastic containers. Urine samples were obtained by cleansing the skin as described above and applying a standard plastic urine-collection bag. Before 24-hour samples were collected, the bag was put in place, and urine was continuously drawn from the bag during the 24-hour period.

Specimens of bone were collected in the autopsy room and immediately frozen in plastic containers. They were later cleanly dissected, and the surface tissue that was adherent or contaminated was discarded. Twelve of the bone specimens were from the vertebral body, and eleven were from the iliac crest. All vertebral specimens were from infants who died acutely without prolonged

Table 1. Plasma and Urinary Aluminum Levels in 18 Premature Infants Receiving Parenteral Nutrition.*

Infant No	Gestation	Birth Weight	Age	Feeding	Plasma Aluminum	Urinary Aluminum	Urinary Excretion of Aluminum	Urinary Aluminum: Creatinine
	wk	g	days		μg/liter		μg/24 hr	
1	28	1070	1	IV	49	29		
			22	BM/F	3	35	5.0	4.3
2	28	980	1	IV	26	260		
			22	BM/F	6	28	2.9	2.2
3	32	1060	1	IV	9	170		
			18	BM/F	9	60	10.1	4.3
4	26	760	1	IV	9	35		
			22	F	26	40	5.3	6.0
5	32	1200	1	IV	3	6		
			25	F	3	8	1.8	0.5
6	30	1460	1	IV	<2	20		
			33	F	6	137	19.5	11.4
7	33	1610	1	IV	<2	15		
			21	F	<2	<2	<2.0	0.2
8	34	1440	1	IV	<2	7		
			23	F	<2	20	3.9	1.8
9	31	1980		IV	9	35		
			24	F	3	20		1.7
10	32	1520	42	F	4	22		
			78	F	13	20	4.7	2.2
11	32	1220	17	F	46	32		
			38	F	13	16	3.5	1.6
12	28	820	16	F	3	25		2.1
			37	F	6	32		2.9
13	36	2720	11	IV	39	42		3.6
			22	F	26	15	4.0	0.9
14	37	2320	22	IV	29	90		9.8
			45	IV	29	85		9.6
15	27	750	30	IV	32	30		3.4
			51	IV	23	105		13.5
16	28	990	22	IV	20	40		5.9
			46	F	4	75		3.1
17	32	1100	16	IV	172	145		14.5
			43	F	9	23	3.8	1.9
18	33	2608	16	IV	136	68		6.7
			32	F	6	132	27.4	11.0

*Aluminum was measured on two different occasions separated by an interval of three weeks. IV denotes intravenous, BM breast milk, and F formula. To convert aluminum values to micromoles per liter, divide by 27.

intravenous therapy. Concentrations of aluminum in vertebral bone were not significantly different from levels in iliac-crest bone (2.25±1.40 vs. 1.92±1.44 mg per kilogram of dry weight). Therefore, the results of the bone analysis are reported without designation of the type of bone. Since normal bone histology has not been well documented in premature infants, histologic studies of bone were not performed in this study.

Plasma, bone, and urine were processed and analyzed for aluminum content, as previously described, by flameless atomic-absorption spectrophotometry.[10] Urinary and serum creatinine levels were determined by standard methods.

Creatinine clearances were corrected for body weight at the time of the 24-hour urine collection. Mean values of aluminum were calculated from the higher plasma and urinary concentrations recorded for each child, if two values were obtained. Aluminum:creatinine ratios were calculated as micrograms per liter of aluminum divided by milligrams per deciliter of creatinine, to derive a number that factored out differences in concentration. Possible sources of aluminum (Tables 4 and 5) were investigated by obtaining aliquots of medications and solutions from pharmacies or formula packages. Breast milk was collected from mothers instructed to cleanse the skin carefully and express milk directly into plastic containers.

Statistical analyses were done by both parametric and nonparametric methods (Student's t-test and the Mann–Whitney U test). Values are expressed as means ±S.D. P values are derived from Student's t-test unless otherwise designated.

Table 3. Urinary Aluminum Levels in Five Infants Receiving Intravenous Therapy for at Least Two Weeks before the Study.*

Infant No.	Age	Weight	Aluminum Intake	Urinary Aluminum	Estimated Retention	Urinary Aluminum:Creatinine
	mo	kg	μg/24 hr		%	
1	5.5	7.8	121	35	71	4.4
2	1.5	3.3	53	21	60	5.5
3	9.0	6.5	103	25	76	2.6
4	4.5	6.7	108	14	87	3.5
5	5.0	6.0	108	5	95	0.7

*To convert aluminum values to micromoles per liter, divide by 27.

Results

Table 1 shows the data on the premature infants with a history of intravenous therapy (Group I), including gestational age, birth weight, and age at the time of the plasma and urinary aluminum determinations, along with the type of intake at the time of measurement. Table 2 shows the data on normal infants without parenteral exposure (Group II). Plasma aluminum levels and urinary aluminum:creatinine ratios were significantly higher in Group I than in Group II: plasma aluminum, 36.78±45.3 vs. 5.17±3.1 μg per liter (1.4±1.7 vs. 0.19±0.11 μmol per liter) ($P<0.0001$); aluminum:creatinine ratio, 5.4±4.6 vs. 0.64±0.75 ($P<0.01$). Plasma aluminum levels and urinary aluminum:creatinine ratios in these two groups are summarized in Figure 1. The previously published normal plasma concentration in adults[10] is 6±3 μg per liter (0.22±0.11 μmol per liter), which is not significantly different from the level in our normal infants. Aluminum concentrations in the 35 umbilical-cord plasma samples were also not significantly different from the levels in normal infants (4.5±3.7 μg per liter [0.17±0.14 μmol per liter]). Although toxic concentrations of aluminum in plasma have not been definitively established, a value over 100 μg per liter is consistently found in association with bone and neurologic abnormalities.[12,16-18] Although the mean value in our infants in Group I was 36 μg per liter, Infants 17 and 18 had values of 172 and 136 μg per liter (6.4 and 4.4 μmol per liter), respectively, which were well into this presumably toxic range.

In 13 Group I patients plasma aluminum concentrations were measured while the infants were receiving intravenous therapy and then while they were receiving formula. Plasma concentrations during intravenous therapy were significantly different from the levels during formula feedings: 36.18±54.57 vs. 8.08±8.2 μg per liter (1.4±2.0 vs. 0.3±0.31 μmol per liter; $P<0.01$, Mann–Whitney U test). There was no correlation between the total number of days of intravenous therapy and subsequent urinary aluminum:creatinine ratios ($r = 0.41$). Interestingly, urinary aluminum concentrations and aluminum:creatinine ratios continued to be very high in some infants (Table 1, Infants 1, 3, 6, and 18), as compared with normal values, even though the infants had not received intravenous therapy for a mean of 13 days and had normal plasma aluminum concentrations. In very premature infants, weight-

Table 2. Plasma and Urinary Aluminum Levels in Eight Normal Term Infants without Exposure to Parenteral Therapy.*

Infant No.	Age at Study	Feeding	Plasma Aluminum	Urinary Aluminum	Urinary Aluminum:Creatinine
			μg/liter		
1	1 day	H_2O	6	15	
	23 days	H_2O/BM	10	70	2.4
2	1 day	F	3	9	
	21 days	F	<2	5	0.6
3	1 day	F	10	12	
	21 days	F	3	15	0.8
4	1 day	F	3	28	
	22 days	F	3	2	0.1
5	9 mo	F		20	0.13
6	2 mo	H_2O/BM		22	0.2
7	7 mo	F		7	0.6
8	3 mo	BM		12	0.28

Table 4. Levels of Aluminum in Commonly Administered Intravenous Solutions.*

Solution	No. of Lots Tested	Aluminum Content (μg/liter)
Potassium phosphate (3000 mmol/liter)	3	16,598±1,801
Sodium phosphate (3000 mmol/liter)	1	5,977
Calcium gluconate (10%)	5	5,056±335
Heparin (1000 units/ml)	3	684±761
Heparin (5000 units/ml)	1	359
Heparin (10,000 units/ml)	1	468
Normal serum albumin (25%)	4	1,822±2,503
Intralipid	1	195
TPN solution (2¼% essential amino acid)	6	72±59
5% Dextrose	2	72±1
Sodium chloride (4000 mmol/liter)	3	6±4
Potassium chloride (3000 mmol/liter)	1	6

*TPN denotes total parenteral nutrition. To convert aluminum values to millimoles per liter, divide by 27. Plus–minus values are means ±S.D.

as low as 20 per cent of those in mature infants (Fig. 2). Weight-corrected creatinine clearances were directly correlated with gestational age, and by 34 weeks had reached normal adult levels (1.7 ml per minute per kilogram of body weight, Fig. 3). The highest plasma aluminum level in these infants did not correlate with creatinine clearance, suggesting that the intake of aluminum is the more important variable.

Group III infants had been receiving intravenous therapy for at least two weeks when aluminum intake and excretion studies were performed: four infants were studied for three days, and one was studied for two days (Table 3). All five infants had negligible stool output. Although stool aluminum was not measured, previous studies have shown that fecal aluminum losses are small in patients receiving parenteral nutrition.[19] Aluminum intake was calculated from concentrations in matched solutions. The five infants had a mean intake of 98.6±11.56 μg (3.6±0.43 μmol) per 24 hours, with a mean excretion of 20.0±5.1 μg (0.74±0.19 μmol) per day, or 78 per cent retention. Normal adult urinary excretion of aluminum is 13±6 μg (0.48±0.22 μmol) per day.[10] The aluminum:creatinine ratio was 3.3±0.08, which is significantly different from the value in normal infants: 0.64±0.75 ($P<0.01$).

Bone aluminum content in Group V (infants who had received intravenous therapy for over three weeks) was significantly higher than in Group IV (those who had received little or no intravenous therapy): 20.16±13.4 vs. 1.98±1.44 (0.75±0.49 vs. 0.07±0.05 mmol) per kilogram of dry weight ($P<0.0001$, Fig. 3). All except one infant treated with long-term parenteral nutrition died during intravenous therapy. The infant who was discharged and died two months later from the sudden infant death syndrome had a bone aluminum concentration of 7 mg (0.26 mmol) per kilogram of dry weight — three times the normal level in infant bone. The normal bone concentration in adults[10] is 3.3±2.9 mg (0.12±0.11 mmol) per kilo-

Tables 4 and 5 list the concentrations of aluminum in commonly used intravenous and oral solutions. Calcium and phosphate salts, heparin, and normal serum albumin have very high concentrations of aluminum, although there is wide variation among lots. Soy and premature-infant formulas with the highest additives of calcium and phosphate salts also have the highest aluminum concentrations. Human breast milk has the least aluminum.

Among the infants in Groups I and II, there was no correlation between plasma and urinary aluminum and the type of formula they were receiving at the time of the study. None of our infants were receiving soy formula, which has the highest concentration of aluminum. It should be noted that normal adult concentrations of urinary aluminum[10] would give an aluminum:creatinine ratio of 0.1; thus, the ratio of 0.6 in our normal infants may reflect the fact that infants absorb aluminum differently from adults.

Discussion

Eight per cent of the earth's crust is composed of aluminum. Human beings are exposed to this element constantly through ingestion of water, food, and dust particles. In fact, it is estimated that an average adult ingests 3 to 5 mg of aluminum per day[20,21] and excretes 14 μg per day in urine — presumably the amount absorbed — leaving only a small level of aluminum in the body.[10] Since the gastrointestinal tract, skin, and lung provide excellent barriers to aluminum absorption and the kidney is efficient in eliminating any absorbed aluminum, the body burden of aluminum in normal persons is exceedingly low. Nonetheless, excessive aluminum accumulation can

Table 5. Levels of Aluminum in Commonly Used Oral Solutions.*

Solution	No. of Lots Tested	Aluminum Content (μg/liter)
Glucose water	1	20
Tap water (Colorado)	1	12
Well water (Colorado)	1	5
Breast milk	12	9.9±6.87
Cow's milk–based formula (20 kcal/30 ml)	4	266±192
Cow's milk–based formula, "premature" (24 kcal/30 ml)	4	699±321
Soy formula (20 kcal/30 ml)	4	1478±103
Multivitamins (liquid)	1	32
Nystatin	1	72

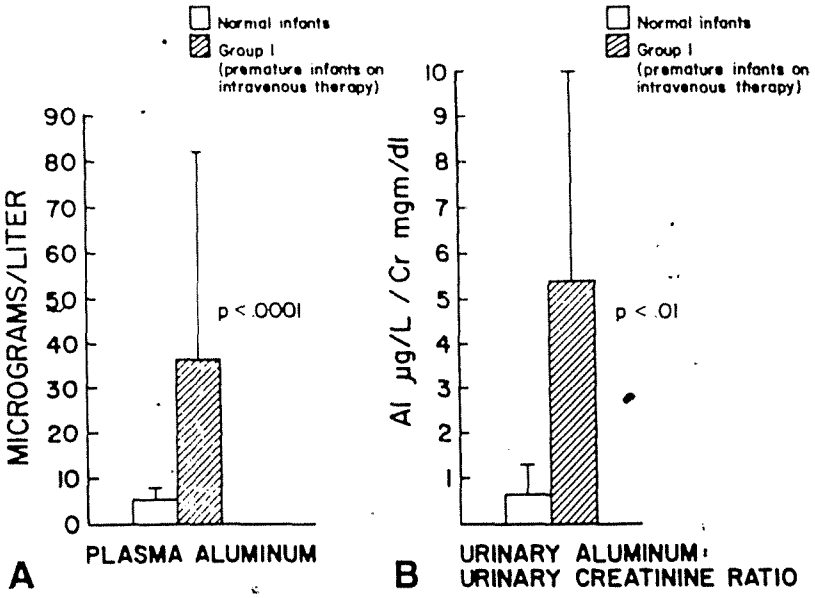

Figure 1. Plasma Aluminum Levels (A) and Urinary Aluminum:Creatinine Ratios (B) in Normal Infants (Group II) and Premature Infants Receiving Intravenous Therapy (Group I).

Bars denote S.D. The normal values in adults are 6±3 µg per liter and 0.1, respectively. Al denotes aluminum, and Cr creatinine. To convert aluminum values to micromoles per liter, divide by 27.

occur and has been reported with both parenteral and oral exposure. Parenteral exposure has resulted in accumulation in patients receiving dialysis with aluminum-contaminated dialysate[6,20] and in those receiving long-term parenteral nutrition with aluminum-contaminated fluids.[14,15] Patients with chronic renal failure receiving large oral loads of aluminum in the form of phosphate-binding gels have also been found to have an increased body burden of aluminum.[12,13,16,22]

Our study concerns another type of patient at risk for aluminum toxicity — the premature infant who is receiving intravenous therapy. Two conditions may predispose such children to aluminum loading: parenteral aluminum exposure and reduced renal function. A number of components of parenteral fluids given to premature infants, such as the calcium and phosphate salts used as additives and human albumin, have high concentrations of aluminum.

Evidence of aluminum loading in premature infants is based on our finding that aluminum in plasma or urine or both was almost uniformly increased in infants receiving parenteral therapy. Moreover, balance studies showed that the infants excreted only about 23 per cent of the intravenously administered aluminum. Additional evidence for aluminum loading comes from the finding that urinary aluminum concentrations remained well above the range found in control infants for several weeks after the termination of parenteral feeding. This finding suggests a slow unloading of tissues.

was 10 times higher than normal in a small group of infants who died after receiving parenteral therapy for three weeks or more.

The amount of toxicity that results from parenterally administered aluminum remains to be determined. The classic manifestations of systemic aluminum intoxication include fracturing osteomalacia, encephalopathy, and microcytic hypochromic anemia.[6,7,23] For a variety of reasons, it is difficult to relate any of the abnormalities found in ill premature infants to aluminum intoxication. Although bone disease is common, the histologic data required for the diagnosis of osteomalacia are nonexistent for premature infants. In addition, metabolic encephalopathy is a common complication of many of the other events that occur along with prematurity, including hypoxia, acidosis, and electrolyte imbalances. Finally, premature infants frequently require multiple transfusions to replace iatrogenic blood loss, precluding definitive hematologic evaluation. The facts that plasma aluminum levels in two infants exceeded

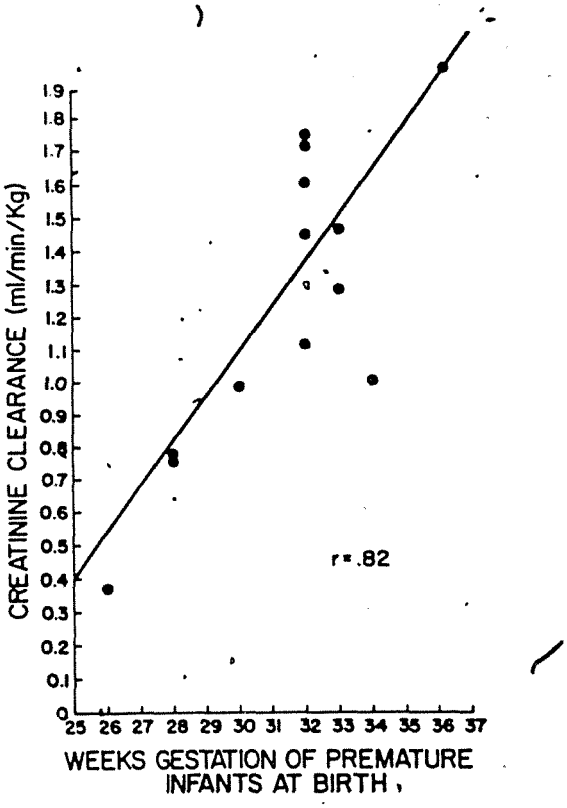

Figure 2. Correlation between Creatinine Clearance Corrected for

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