Aluminum Toxicity in Infants and Children

During the last 15 years, accumulating evidence has implicated aluminum in disorders associated with chronic renal failure. The well-recognized manifestations of systemic aluminum toxicity include fracturing osteomalacia, dialysis encephalopathy, and microcytic hypochromic anemia. More recently, aluminum loading has been demonstrated in premature infants receiving intravenous fluid therapy. Although the clinical importance of this finding is unclear, it warrants careful attention. The association between aluminum excess and neurologic dysfunction, which has been reported in patients with chronic renal failure, suggests the possibility that aluminum overload may contribute to the pathogenesis of CNS damage in the sick premature infant.

ALUMINUM EXPOSURE

Aluminum, which is the most abundant metal in the earth’s crust, is ubiquitous in its distribution. There is constant exposure to this element through ingestion of water and food and exposure to dust particles. Because aluminum sulfate (alum) is used as a flocculating agent in the purification of municipal water supplies, drinking water may contain high levels of aluminum (up to 1,000 μg/L). Aluminum cans, containers, and cooking utensils, as well as aluminum-containing medications, are also potential sources of oral intake of aluminum. Increase in aluminum intake as a result of transfer through the skin is probably negligible; however, exposure is common due to use of aluminum in deodorants. Some inhaled aluminum is retained in pulmonary tissue and in the peribronchial lymph nodes, but it is largely excluded from other tissues. Pulmonary aluminum concentration increases with age; unlike aluminum levels in other tissues, the concentration in the lung does not correlate with that in other tissues.

Average adult intake of aluminum is probably 3 to 5 mg/d of which about 15 μg (0.3% to 0.5%) is absorbed. Most, if not all, of the absorbed aluminum is normally excreted in urine, leaving a total body aluminum level at less than 30 to 40 mg. When an individual with a normal glomerular filtration rate increases aluminum intake by ingestion of aluminum-containing antacids, there is increased absorption and urinary excretion of aluminum.

Although the renal handling of aluminum has not been well defined, the normal individual appears capable of increasing renal aluminum clearance from approximately 5% to about 50% of glomerular filtration rate. The low aluminum clearance normally present is largely related to the plasma binding of aluminum by a saturable plasma component at blood levels less than 200 μg/L.

Tissue aluminum levels are consistently low in persons with normal renal function who have ingested large amounts of aluminum-containing antacids for years. However, in individuals with chronic renal failure, total body aluminum can be markedly increased. The tissues most frequently affected and having the highest aluminum concentrations are bone and liver.

In 1976, Alfrey and associates published data showing that brain tissue of patients dying from a neurologic syndrome called dialysis encephalopathy had high concentrations of aluminum in the gray matter. Two years later, European investigators noted that a severe form of osteomalacic osteodystrophy (fracturing dialysis osteodystrophy) and dialysis encephalopathy occurred together in large numbers of patients undergoing dialysis with dialysate prepared from tap water that contained large amounts of aluminum. The epidemic-like occurrence of these diseases was largely eliminated by removing aluminum from the water used to prepare dialysate (ie, aluminum concentration reduced to less than 10 μg/L). The first reports of pediatric patients with a progressive encephalopathy similar to dialysis encephalopathy described children who had not received dialysis at the time their symptoms first appeared. Five children with severe renal failure secondary to congenital renal disease had a progressive encephalopathy. They had received doses of aluminum-containing phosphate binders as high as 240 to 800 mg/kg/d for periods of 4 to
12 months. Subsequently, from an international survey of pediatric dialysis facilities, 24 children with an unexplained form of encephalopathy were found. Many of these children had not received any form of dialysis but had been treated with aluminum-containing phosphate-binding gels. Since these earlier reports, both dialysis encephalopathy and aluminum-related osteomalacic osteodystrophy have been described in infants, children, and adults with chronic renal failure prior to initiation of dialysis. The earlier reports did not include data on plasma and tissue aluminum levels.

**ALUMINUM-ASSOCIATED DISEASE**

In 1984, Andreoli and associates reported the occurrence of aluminum-associated bone disease in three infants with azotemia who did not receive dialysis but had been treated with aluminum hydroxide from the first month of life. The infants' serum aluminum levels were significantly elevated, and biopsies of the iliac crest demonstrated severe osteomalacia and massive deposition of aluminum in bone. In the same year, Sedman and associates described a child who had chronic renal failure and normal neurologic findings at 2 years of age and encephalopathy when 8 years of age. This child had not received dialysis but had received aluminum-containing phosphate binders for 6 years. High concentrations of aluminum were found in serum samples and bone biopsy specimens. Two other studies of children with chronic renal failure reported aluminum loading in 33 children receiving phosphate binders for 6 years. Serum aluminum concentrations were increased in all instances, and bone aluminum levels confirmed aluminum loading in five instances. The oral route was assumed to be the source of aluminum because the infused dialysate aluminum concentration was negligible in the 23 patients receiving peritoneal dialysis and because tap water aluminum levels were not contributory in the seven children receiving hemodialysis. In the data from these two studies, as well as that of Andreoli and associates, there is a dose-dependent correlation between elemental aluminum administered orally to infants and children with chronic renal failure and plasma aluminum concentrations.

**CHRONIC RENAL FAILURE**

Recent studies on aluminum loading and aluminum intoxication in infants and children with chronic renal failure indicate that orally administered aluminum-containing phosphate-binding gels are probably the source of the excess aluminum burden. The risk of aluminum intoxication appears to be greatest in infants and young children because of the large quantity of aluminum-containing binder (per kilogram of body weight) needed to control hyperphosphatemia. Adults usually consume less than 30 mg/kg/d of elemental aluminum for phosphate binding. In contrast, infants and children with severe chronic renal failure have often required aluminum at doses of 100 mg/kg/d or more to control hyperphosphatemia and secondary hyperparathyroidism.

A recent study has shown that calcium carbonate is as effective as aluminum hydroxide in the control of secondary hyperparathyroidism in children with chronic renal failure. The current recommendations for the management of secondary hyperparathyroidism in pediatric patients include limitation of phosphorus intake, the use of calcium carbonate as a phosphate binder, and supplementation with a vitamin D metabolite or its equivalent. Aluminum-containing phosphate binders should be used only when the calcium binder cannot be tolerated or because of hypercalcemia. Because a safe dosage is yet to be determined, elemental aluminum doses should probably not exceed 30 mg/kg/d. Aluminum-free oral phosphate binders are currently being studied in Europe. These are natural polymers consisting of heteropolyuronides charged with calcium and iron cations. Iron-containing preparations trap phosphate under acidic conditions, whereas, with neutral or alkaline pH, the calcium phosphate formed is partially trapped in the matrix of the polymer.

**ALUMINUM LOADING IN INFANTS**

Sedman and associates found high concentrations of aluminum in bone, urine, and plasma of infants receiving intravenous therapy. Significantly higher plasma and urinary aluminum concentrations were observed in 18 premature infants admitted to an intensive care unit and treated with intravenous therapy than were found in eight term infants who were not given intravenous fluids. Thirteen of the premature infants receiving intravenous fluids had a second plasma aluminum measurement after an interval of 3 weeks while receiving formula. Plasma aluminum concentrations for infants receiving intravenous fluid therapy were significantly higher than those for infants receiving formula feeding (36.18 ± 54.57 µg/L vs 8.08 ± 8.2 µg/L). As shown in Table 1, albumin and a number of substances frequently used as additives in the parenteral fluids given to premature infants have high aluminum concentrations. (The literature contains...
only scant data on the concentration of aluminum in additives frequently used in intravenous solutions\(^7,28\) (Table 1) and in infant feeding mixtures\(^7,29\) (Table 2). The lack of data appears to be a consequence of technical problems related to the measurement of relatively low concentrations of aluminum in an environment in which the distribution of aluminum is ubiquitous. Sedman et al\(^7\) performed two-day and three-day urinary balance studies on five infants who had been receiving intravenous fluid therapy for at least 3 weeks. Stool losses were reported as negligible during the balance periods. The infants' daily excretion of aluminum was about 20\% of that administered intravenously. Sedman et al. also included data on bone aluminum concentrations from autopsy specimens collected from 23 infants, six of whom had received at least 3 weeks of parenteral nutrition. These six infants were less than 37 weeks of gestation. Bone aluminum concentration was ten times higher in the six infants who had received at least 3 weeks of intravenous fluid therapy than in the 17 infants who had received limited intravenous fluid therapy. Sedman and associates concluded that aluminum loading occurred in premature infants as a result of the combination of contamination of fluids given in intravenous treatment and poor renal clearance of aluminum.

The studies cited indicate that excessive aluminum accumulation may occur in patients with renal failure who receive dialysis with aluminum-contaminated dialysate and in premature infants with reduced renal function given aluminum-contaminated intravenous fluids\(^17\). Aluminum loading has been observed in patients who have normal renal function and who receive long-term parenteral nutrition with aluminum-contaminated fluids\(^30-32\) and in patients with chronic renal failure who ingest aluminum-containing phosphate-binding gels.\(^17-25\) Recently, Freundlich and associates\(^29\) reported two neonates with renal failure in whom the aluminum present in proprietary infant milk formulas appeared to play a role in the development of aluminum toxicity. Neither infant had received oral alu-
minum-containing phosphate binders or intravenous fluids. The larger infant, with a birth weight of 3,300 g, was treated with peritoneal dialysis from 2 weeks of age until death during the third month. The second infant, who weighed 1,700 g at birth, died after 1 month of conservative management without dialysis. Both infants received enteral alimentation using a low-solute milk-based infant formula. The diagnosis of aluminum toxicity in these infants was based on postmortem tissue analyses. Aluminum content of brain tissue from the larger infant was 6.4 μg/g in gray matter and 0.4 μg/g in white matter (normal < 0.1 μg/g). Brain aluminum content was 47.4 μg/g in the smaller infant. Neither infant had stainable aluminum in bone or increased bone aluminum content. Data on the aluminum content of human milk and a variety of infant-feeding mixtures are shown in Table 2. The infants reported by Freundlich et al29 had been given enteral alimentation using Similac PM 60/40. The diagnosis of aluminum loading. Careful clinical and biochemical monitoring are warranted to determine whether it will be necessary to eliminate aluminum contamination of both oral and parenteral preparations used with infants and children who may be at risk for aluminum intoxication.

Deferoxamine administered intravenously has been shown to reduce the body aluminum burden and ameliorate injury to bone and brain in adults receiving hemodialysis and peritoneal dialysis.33-35 Andreoli and associates36 reported successful treatment of severe aluminum-related encephalopathy in a 7½-year-old child receiving chronic peritoneal dialysis. The deferoxamine was added to each bag of dialysate and administered with the usual exchanges. Although new cases of aluminum intoxication should be preventable in most instances, deferoxamine therapy appears beneficial for those with established toxicity.

CONCLUSIONS

Dialysis encephalopathy and fracturing osteomalacia, which occurred preponderantly in hemodialysis units using dialysis fluid contaminated with aluminum, have largely disappeared since standards for safe concentrations of aluminum in dialysate have been established. Infants, children, and adults with chronic renal failure who are not receiving dialysis have been shown to be at risk for aluminum intoxication from oral administration of aluminum-containing phosphate binders. This complication should be avoidable with the use of phosphate binders that do not contain aluminum and the use of other measures to control hyperphosphatemia.

Drinking water in certain communities and some infant formulas may contain relatively high concentrations of aluminum. The reported concentration of aluminum in soy formulas is higher than in other infant-feeding mixtures tested. These substances may be a significant source of aluminum in the diet of low birth weight infants and in infants and young children with impaired renal function.

A number of substances commonly administered intravenously, including calcium and phosphorus salts and albumin, have high levels of aluminum. Premature infants receiving intravenous fluid therapy show evidence of aluminum loading. Careful clinical and biochemical monitoring are warranted to determine whether it will be necessary to eliminate aluminum contamination of both oral and parenteral preparations used with infants and children who may be at risk for aluminum intoxication.
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