Aluminum Toxicity in Relation to Kidney Disorders

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ABSTRACT

Aluminum toxicity in patients with chronic renal failure has been related to renal osteodystrophy and dialysis encephalopathy (DES). The toxicity is associated with renal osteodystrophy in two ways. One association is the iatrogenic effect of excessive use of aluminum hydroxide gels resulting in hypophosphatemia which interferes with bone mineralization. The second association may involve deposition of aluminum in bone owing to aluminum being absorbed during hemodialysis. Evidence for this second association has been gathered from epidemiological studies of hemodialysis centers and their practices of using either tap water high in aluminum in the dialysate, or aluminum-free deionized water. In patients with DES, aluminum accumulation in the brain has been clearly shown to come from either the ingestion of aluminum containing phosphate-binding gels, aluminum in the dialysate, or a combination of the two. The outbreak of the DES also has been well-correlated with the sudden elevation of aluminum in tap water owing to the use of large amounts of aluminum in water treatment plants. Whether aluminum itself or a combination of aluminum and other factors causes DES is not understood at this time.

Introduction

Aluminum toxicity has been implicated in the pathogenesis of a number of clinical disorders in patients with chronic renal failure on long-term intermittent hemodialysis treatment. The predominant disorders have been osteomalacic dialysis osteodystrophy and dialysis encephalopathy. The findings implicating aluminum in these two disorders are reviewed here.

Renal Osteodystrophy

There are several types of osteodystrophy associated with chronic renal failure which include osteitis fibrosa cystica, osteosclerosis, osteoporosis, and osteomalacia. Osteomalacia is a condition marked by softening of the bone and increased flexibility which can often lead to spontaneous fractures. This condition occurs when there is an impairment in the bone mineralization process. Patients on
long-term hemodialysis for chronic renal failure tend to retain phosphate which can cause both ectopic calcifications and osteitis fibrosa cystica. These patients are given aluminum hydroxide orally to control their hyperphosphatemia. Over-treatment with aluminum hydroxide gels may result in a hypophosphatemia. In this manner, the oral aluminum treatment can interfere with bone mineralization and result in osteomalacia.

Dent et al. reported that the oral administration of aluminum hydroxide could cause a decrease in plasma phosphorus levels. This effect of aluminum hydroxide on plasma phosphorus levels was also demonstrated by Clarkson et al. and Cam et al. From these studies, it is apparent that a prolonged hypophosphatemia does result from the long-term use of large doses of aluminum hydroxide to control plasma phosphate levels in chronic renal failure patients.

Osteomalacia owing to severe phosphate depletion in a patient with normal renal function was reported by Dent and Winter. The patient presented with bone pain, weakness, difficulty with walking, and abnormal plasma alkaline phosphatase, calcium, and phosphorus. The history of the patient revealed a chronic use of antacids for 15 months during which time the patient consumed up to 11.4 grams of aluminum daily. The patient was treated with a phosphate repletion diet and completely recovered. This type of osteomalacia (hypophosphatemic) is characterized by low plasma phosphorus, possibly elevated alkaline phosphatase, and a high calcium and low phosphorus concentration in the urine.

A renal dialysis patient with osteomalacia owing to hypophosphatemia was reported by Baker et al. After almost two years of dialysis, this patient complained of bone pain and weakness. She had an elevated plasma alkaline phosphatase activity with an increased concentration of calcium and decreased phosphate in the plasma together with Looser's zones in the pelvis on radiological examination. Six weeks after aluminum hydroxide was stopped and a phosphate enriched diet started, the bone pain and muscle weakness was absent. X-rays revealed healing of the Looser's zones.

These two cases illustrated the potential hazard of aluminum-containing antacids in both people with normal renal function and those with chronic renal failure.

Osteomalacia, in the chronic renal failure patient, may also result from the aluminum absorbed during hemodialysis and deposited in bone. The correlation between this type of osteomalacia and aluminum is not as clearly understood as that resulting from hypophosphatemia owing to the excess ingestion of aluminum gels.

In a study of 202 dialysis patients, Platts et al. found 11 patients with multiple fractures and 10 patients with single fractures. All of these fractures occurred after the patients had begun hemodialysis. In most cases, the fractures did not appear until several years after dialysis was begun. The uneven geographical distribution of the fracture patients, as well as the patients with no fractures, led Platts et al. to investigate the water supplies used for hemodialysis. The home tap water used by the patients with fractures had a lower concentration of calcium and fluorine and a higher level of aluminum and manganese than the water used by the hemodialysis patients with no fractures. Also, the patients with multiple fractures were dialyzed against water that contained higher aluminum and manganese levels than those patients with a single fracture. Aluminum hydroxide ingestion was not considered a contributing factor in these fractures because only four patients took the gel, and they did not do so consistently.

In a similar study, Ward et al. reported a correlation between water aluminum levels and osteomalacia. The incidence of osteomalacia was more prevalent in the areas with higher aluminum content in
the tap water used to make up the dialysate. In a comparison between patients dialysed using deionized water versus a group using tap water treated with a water softener, the authors report that all nine patients using tap water developed osteomalacia within three years of starting hemodialysis; only two of eight patients using deionized water developed osteomalacia within four years of hemodialysis treatment.

The reports by Parkinson et al.33 and Ward et al.41 provide direct evidence for a link between aluminum and a disruption of the bone mineralization process. A more direct approach used by Cournot-Witmer et al.17 revealed a correlation between increased osteoid volume and increased bone aluminum content. Although aluminum appears to interfere with normal bone mineralization, the effect(s) upon this process are not understood.

Dialysis Encephalopathy Syndrome (Dialysis Dementia)

In 1972, a neurological syndrome occurring in patients on chronic hemodialysis was described by Alfrey et al.3 The syndrome included dementia, speech difficulties, motor abnormalities, and electroencephalographic changes. In all of the patients, the syndrome started with a speech disorder and progressed to marked motor abnormalities, personality changes and, in some cases, a severe psychosis developed. As the disease progressed, some patients lost muscle coordination and had severe seizures. With further progression, the patient was incapacitated and, ultimately, the disease was fatal.

Owing to the rapid onset of the syndrome, Alfrey and his co-workers suspected that a toxin was present in the untreated tap water used for dialysis. Since several heavy metals (lead, arsenic, copper, etc.) can cause encephalopathies, trace metal analyses were performed on the brains of patients who died with this syndrome. The most important difference found at that time was the increased tin level in the brain of some uremic patients; the source of the elevated tin levels was not clear. A later report also mentioned elevated tin at levels in the brains in chronic dialysis patients with progressive encephalopathy.12

Since Alfrey et al.3 first described the neurological syndrome in 1972, several other dialysis centers throughout the world have reported the occurrence of patients with the same symptoms. These include Burks et al. (USA),12 Barratt and Lawrence (Australia),7 Wardle (United Kingdom),40 and Mahurkar et al. (USA).28 Wardle suggested that dopamine, an important neurotransmitter, may be removed during dialysis, creating a deficiency state40; however, if this were true, a more prevalent occurrence of this syndrome in dialysis patients would be suspected. Other possible etiological agents which have been postulated include a virus7,14 and altered cerebrospinal fluid dynamics,27 although no substantial experimental evidence has been reported to support these theories.

The studies on serum and bone aluminum reported by Berlyne et al.8 Parsons et al.34 and Clarkson et al.16 prompted Alfrey and co-workers to study aluminum levels in tissue in both control and uremic patients. This investigation was published by Alfrey et al.2 in 1976 and showed elevations in aluminum levels in muscle, bone, and brain gray matter of uremic patients when compared with control subjects. Alfrey and co-workers proposed that aluminum was a possible etiological agent in the dialysis encephalopathy syndrome.

The role of aluminum as an etiological agent was supported by the fact that the syndrome first occurred at an interval of 2.5 years from the commencement of the use of aluminum phosphate-binding gels. Most patients who developed the syndrome had been on dialysis and aluminum-containing gels for over three years. Since the aluminum level in the dialysate was "negligible" and the transfer of aluminum across the dialysis mem-
brane could not be demonstrated, the authors suggested that the elevated tissue aluminum came from the aluminum phosphate-binding gels.

After Alfrey et al.\(^2\) published their paper implicating aluminum, many renal centers with patients suffering from the dialysis encephalopathy syndrome (DES) investigated the aluminum levels in their patients, as well as searched for the source of the aluminum. A unique source of aluminum contamination in the dialysate was reported by Flendrig et al.\(^24\) In their dialysis unit, water used to make the dialysate was heated in a boiler equipped with an aluminum cathodic protection device. It was found that the aluminum anode was slowly dissolving and raising the aluminum level in the water to a higher concentration than that in the untreated tap water. After conversion to a different system, the patients showed signs of improvement.

Several other groups have reported sudden outbreaks of DES.\(^10,26,29,31,37\)

McDermott et al.\(^31\) reported seven cases of DES in 19 dialedy patients. More importantly, they correlated the level of aluminum in brain gray matter with the duration of hemodialysis treatment using softened or untreated tap water to make up the dialysate. Patients who were switched from softened or untreated tap water to deionized water showed a less positive correlation owing, undoubtedly, to the lower aluminum concentration in the dialysate made from deionized water. The authors were unable to demonstrate any correlation between the brain aluminum content and the ingestion of aluminum containing phosphate-binding gels.

Dunea et al.\(^20\), Mahurkar et al.\(^29\) and Rozas et al.\(^37\) all reported DES in their patients. This was associated with a high aluminum content of the water used to make up the dialysate. In all three reports, the elevated aluminum was correlated with the use of aluminum sulfate as a flocculant in the city water treatment systems. The outbreaks of DES reported by two of the groups occurred only after the city water treatment began to use aluminum sulfate which increased the tap water aluminum level to as high as 400 μg per L.\(^29,40\) In all cases, the occurrence of DES was reduced or eliminated by the use of deionized water in the preparation of the dialysate.

Further implications of aluminum as the etiological agent were provided by the epidemiological studies of Platts et al.\(^35\), Elliott et al.\(^21\) and Parkinson et al.\(^33\), Platts et al.\(^35\) in the Trent Region of England and Elliott et al.\(^51\) in the west of Scotland correlated the geographical distribution of DES with the elevated water aluminum levels in those areas. Parkinson et al.\(^33\) conducted a survey of 1293 patients in 18 dialysis centers in Great Britain. By comparing mean water aluminum levels and the number of patients at each center with DES, the authors were able to demonstrate a higher incidence of DES at the centers with the most aluminum in the water. Although direct evidence against aluminum was lacking, all the authors recommended the use of deionized water in the hemodialysis procedure. Whether aluminum itself or a combination of aluminum with other factors\(^5\) causes DES is not understood. Much research is needed in this area before the complete biochemical and physiological consequences of aluminum accumulation in brain tissue will be elucidated.

**Treatment for Dialysis Encephalopathy**

An effective treatment for DES has not been described. In most cases the syndrome shows a progressive deterioration and the patient dies. Diazepam has been shown to control the seizure disorders, but its effectiveness is only temporary.\(^3,32,37,38\) Other drugs have been used, but the outcome remains the same.

A reversible DES has been reported by several authors.\(^11,30,36\) Poisson et al.\(^36\) described one patient who showed clinical improvement and was cured one month after...
oral aluminum hydroxide was stopped and the dialysate aluminum level was lowered. Masselot et al.30 and Buge et al.11 reported a reversal of the DES after oral aluminum hydroxide intake was stopped. In these two reports, the DES reappeared when the aluminum gel was again given to the patient and remission occurred a second time when the aluminum gel was stopped. Masselot et al.30 went a step further and used hemofiltration to reduce the serum aluminum level. These cases are isolated reports and are not the usual course of the DES. Explanations as to why these few patients showed a reversal of the syndrome are unclear. Possibly they were diagnosed in an early stage and the reduction of the serum aluminum halted further progression in their neurological symptoms.

Only one case has been described where a patient successfully recovered from the DES following renal transplantation.23 Burks et al.13 found no improvement even with the onset of good renal function, and the neurological condition continued to deteriorate. One patient referenced by Burks et al.13 did show a slight improvement at 1.5 years after a successful renal transplant. The cause of the mixed effect of renal transplants is not understood.

Plasmapheresis was used in an attempt to reduce elevated serum aluminum levels in two patients.23 In both cases some aluminum was removed, but the replacement solution used was later found to contain a high concentration of aluminum which resulted in no net removal of aluminum. The authors stated that even though plasmapheresis can remove some aluminum, the rate, even with aluminum-free replacement solution, was too low to be effective.

Several authors have reported the removal of aluminum from the plasma during dialysis with a low aluminum in the dialysate4,9,23; however, one report24 stated that little or no aluminum was removed from plasma during the dialysis procedure when using a dialysate with a low aluminum content. Both groups used a dialysate of almost equal aluminum content and got opposite results on the post-dialysis plasma aluminum levels. Such contradictions are difficult to explain.

Even though aluminum may be removed by dialysis, this has not been shown to help the patient who has developed the DES. In almost all cases reported, the syndrome is fatal no matter what measures are taken to reverse its course. Since it is now known that aluminum is taken up by body tissues, the only treatment that may really help the DES patient is to find a method that can adequately remove tissue aluminum, especially that stored in the brain.

The evidence relating aluminum to renal osteodystrophy and DES in patients with chronic renal failure is mostly circumstantial. However, there are a considerable number of reports providing positive correlations between exposure to aluminum and incidence of disease, which strongly suggests that aluminum is a toxic agent.

References


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