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Citrate and Aluminum Interaction in Chronic Renal Failure: a Historic Note

Between April and September of 1985 we lost four patients with chronic renal failure who displayed an alarming acute syndrome of obtundation, mutism or dysarthria, ataxia, and myoclonic jerks which rapidly evolved to intractable generalized convulsions, and culminated in circulatory shock refractory to treatment with vasopressor agents. The patients died within one month after admission to the hospital¹. Two of them had not been dialyzed before the onset of the fatal syndrome; and two had just started dialysis the month before. Computerized axial brain tomography and laboratory tests were unremarkable but for the presence of a microcytic anemia and of alarmingly high serum aluminum (Al) levels of 1140, 780, 610 and 380 g/L (mean 727; SD 277; normal: 7; SD 3). Intensive dialysis and chelation with desferrioxamine were not fruitful. Electroencephalographic tracings resembled the pattern seen in the dialysis dementia of the 1970s, caused by high aluminum levels in the water used for making dialysate, and largely gone by the end of that decade as a result of better water purification.

In our attempt to understand why the marked hyperaluminemia occurred in those four patients, we noted that they all had taken not only the phosphate-binder, aluminum hydroxide (AmphogelTM), but also the alkalinizing Shohl's solution, a mixture of sodium citrate and citric acid. We therefore postulated that it was the concomitant intake of citrate and aluminum that facilitated the occurrence of the fatal hyperaluminemia; citrate having enhanced the gastro-intestinal absorption of aluminum. To test the validity of this postulate, we studied pre-dialysis patients and measured serial serum and urine aluminum levels in five healthy subjects, who took aluminum hydroxide for four days, washed out the aluminum from the body for two weeks, then took aluminum hydroxide and Shohl's solution for four days².

Beside the four encephalopathic patients, there were 34 pre-dialysis patients. Seven of the 34 had taken neither aluminum nor citrate (Al 53, SD 53); five, only citrate (Al 59, SD 69); twelve, only aluminum (Al 73, SD 33); and ten had taken both citrate and aluminum (Al 157, SD 83). The mean Al level of each of these subgroups was significantly lower than that of the encephalopathic patients. The latter's mean age (68, SD 14), and aluminum dose (5 g/day, SD 0.9), but not serum creatinine values (11 mg/dL, SD 2.8), were significantly higher than those of the ten non-encephalopathic patients taking both citrate and aluminum (49 years, SD 8; 3 g aluminum/day, SD 1.6; serum creatinine level 10.6 mg/dL, SD 3.8 respectively). Serum Al value of this latter group was significantly higher than that of the 12 patients taking aluminum only, although the two groups showed no significant differences in age, aluminum dose, or serum creatinine concentration. Multivariate regression analysis of the data of all the 38 patients (including the four encephalopathic patients) showed that age, aluminum dose, and concomitant citrate and aluminum intakes had a direct relationship to serum aluminum levels². In the healthy volunteer study², the fractional 24-hour aluminum clearance (aluminum clearance/creatinine clearance x 100) during the concomitant ingestion of citrate and aluminum (6%, SD 3) was significantly greater than that during aluminum ingestion alone (1%, SD 1).

Our findings prompted us to discontinue the practice of prescribing aluminum hydroxide simultaneously with citrate, to give sodium bicarbonate if an alkali was needed, to administer calcium carbonate as a phosphate-binder, and to markedly reduce the dose of aluminum hydroxide,

especially in older patients^{1,2}. We did not encounter any more patients with hyperaluminumemia or encephalopathy after 1985. The above findings were subsequently confirmed by other investigators^{3,4}. Our observations helped to fuel the abandonment of the concomitant administration of citrate and aluminum.

There are several mechanisms by which citrate may enhance aluminum toxicity^{3,4}. Citrate, a tricarboxylic acid, is a strong chelator of aluminum, which, having the dual properties of polyvalence and a small ionic radius, has a strong affinity for citrate, linking to its three carboxyl groups to form a soluble one-to-one hexa-coordinate complex. This enhances aluminum solubility in the less acidic environment of the proximal small intestines, the major site of aluminum absorption. Furthermore, in the rat, citrate, by chelating calcium, opens the tight junctions of the jejunal mucosal cells, thereby enhancing the paracellular absorption of aluminum. Aluminum in the circulation is usually bound to transferrin, but rapid influxes are taken up by small molecular species such as citrate, folate, and ascorbate. Citrate could then act as a carrier for aluminum, delivering it to sites less accessible to transferrin-bound aluminum, such as the brain or the mineralization surface of bone^{3,4}.

Fortunately, with the increasing number of aluminum-free phosphate-binders being commercially available today, the incidence of aluminum toxicity has declined considerably.

References:

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Comments by Todd S. Ing, MD

Dr. Bakir and his colleagues, pioneers in the investigation of aluminum toxicity in renal failure patients, have vividly recounted the story of their very important discovery garnered as a result of immensely astute clinical observations.

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