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Aluminum Overload: An Easily-Ignored Problem in Dialysis Patients with Hyperparathyroidism

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1. Introduction

Dialysis patients are at high risk for aluminum overload, especially patients with hyperparathyroidism, who may occasionally take aluminum-containing phosphate binders. Dialysis patients with aluminum overload may have various symptoms, such as general bone or muscle pain, iron-resistant anemia, hypercalcemia, and neurologic abnormalities, which are sometimes difficult to differentiate from clinical manifestations of hyperparathyroidism. Because of the different therapeutic strategies between aluminum overload and hyperparathyroidism, an overview of aluminum overload in dialysis patients with hyperparathyroidism is presented in the following sections.

2. Aluminum overload in dialysis patients

Dialysis patients are at high risk for aluminum overload (Jaffe, J.A. et al., 2005) because of long-term use of aluminum-containing phosphate binders (Humpfner, A. et al., 1993; Salusky, I.B., 2006), poor renal excretion of aluminum, and contact with aluminum-containing dialysate. Aluminum can be eliminated from dialysate by using reverse osmosis and deionization techniques. The dialysate concentration of aluminum is suggested to be maintained at <10 µg/L (Fernández-Martin, J.L. et al., 1998; National Kidney Foundation [NKF], 2003). Therefore, aluminum-containing phosphate binders had been documented as the predominant source of aluminum exposure in dialysis patients (Savory, J. et al., 1989; Slatopolsky, E., 1987). Because of multiple systemic aluminum-related complications, reducing the exposure of dialysis patients to aluminum by substituting calcium- and other non-aluminum-based phosphate binders is a well-known concept. However, some patients with refractory hyperphosphatemia or calcium-induced hypercalcemia still require aluminum therapy (NKF, 2003). While aluminum-based phosphate binders used as short-term therapy are suggested by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, these medications are prohibited in some countries (Koiwa, F., & Sato, Y., 2009). Non-calcium and non-aluminum phosphate binders (such as sevelamer hydrochloride and

lanthanum carbonate) are suggested as substitutes. However, these newly developed medications have not become popular in many countries because of their high cost (Koiwa, F. & Sato, Y., 2009). In addition, the source of aluminum may contribute to extra aluminum intake from other medications (Bohrer, D. et al., 2009). Therefore, aluminum overload is still a potential problem in the dialysis population.

2.1 Frequency of aluminum overload

The declining exposure of aluminum-containing dialysate and medications with commonly use of high flux dialyzers has resulted in a low incidence of abnormal aluminum levels in current dialysis patients (Cannata-Andía, J.B. & Fernández-Martín, J.L., 2002). In one retrospective study on more than 43,000 dialysis patients, 2.5% of the patients had elevated serum aluminum levels ($>50 \mu\text{g/L}$) that significantly declined year by year (Jaffe, J.A. et al., 2005). However, the prevalence of aluminum overload might be higher in countries that still commonly used aluminum-containing phosphate binders (Kan, W.C. et al., 2010).

2.2 Clinical manifestations of aluminum overload

Aluminum can accumulate in many human organs; this accumulation has been implicated in various diseases, including dialysis encephalopathy, aluminum-induced bone disease (such as osteomalacia), hypercalcemia, and iron-resistant microcytic anemia (NKF, 2003; Berlyne, G.M. et al., 1970, 1972; Sherrard, D.J., 1974; Alfrey, A.C. et al., 1976, 1987; Ward, M.K. et al., 1978; Parkinson, I.S. et al., 1979; Drüeke T., 1980; Hewitt, C.D. et al., 1990). (Summary of Aluminum-related disorders: Features, Causes, and Considerations for therapy, http://www.kidney.org/professionals/kdoqi/guidelines_bone/images/table311.jpg)

2.2.1 Dialysis encephalopathy

Dialysis encephalopathy is usually a slowly progressive disorder with symptoms appearing after a patient has undergone dialysis for 1 year or even longer. Increased aluminum is found in the brain tissue of affected patients (Alfrey, A.C. et al., 1976). It is characterized by myoclonic jerks, mental changes, speech disturbances, visual or auditory hallucinations, paranoid behaviors, and even seizures. These neurologic abnormalities maybe fluctuate and often worsen temporarily after hemodialysis. The typical electroencephalographic (EEG) findings differ from the generalized slow wave with other causes of metabolic encephalopathy (Hughes, J.R. & Schreeder, M.T., 1980). However, due to its insidious progression, diagnosing these neurological disorders depends on clinical observation and suspicion, the finding of elevated plasma aluminum levels, and associated EEG features. New cases of dialysis encephalopathy disappeared after the initiation of water purification in 1979, and no more new cases have been reported in the developed countries since then (NKF, 2003).

2.2.2 Aluminum-induced bone disease

Aluminum can affect normal bone formation via several mechanisms. First, it interferes with mineralization of the matrix by forming crystals to compete for the site of calcium deposition, and it inhibits the activity of osteoblasts, both of which impair bone-building (Jeffery, E.H. et al., 1996). Second, it binds in the parathyroid gland, which inhibits the normal secretion of parathyroid hormone (PTH) (Cannata, J.B. et al., 1988), and it impairs PTH synthesis at the transcriptional level (Díaz-Corte, C. et al., 2001). Because of abnormal

bone formation, osteomalacia is the most frequently seen aluminum-induced bone disease, but its prevalence is reported to have markedly decreased after reduced exposure to aluminum (NKF, 2003). Osteomalacia is characterized by a low rate of bone turnover, a decreased number of bone-forming and bone-resorbing cells, and an increased volume of unmineralized bone (Delmez, J.A. & Slatopolsky, E., 1992; Slatopolsky, E., 1987). In addition, because of its potential to excessively suppress PTH, aluminum overload may cause adynamic bone disease in a minority of cases.

2.2.3 Anemia

Aluminum can also affect normal hemopoietic processes via several mechanisms. First, it impairs intestinal absorption, serum transport, and cellular uptake of iron, because aluminum and iron share a common absorption pathway and, in the serum, they are transported on the same carriers in humans (Kausz, A.T. et al., 1999). These carriers include large proteins (such as transferrin and albumin) and small molecules (such as citrate and phosphate). In several animal and human studies, a significant negative correlation was found between aluminum load and iron transferrin saturation (Cannata, J.B. et al., 1991), and additional reductions in the use of aluminum-containing medications led to significant increases in hemoglobin and reductions in the need for intravenous iron supplementation in hemodialysis patients (Cannata, J.B. et al., 1983a). Second, aluminum may induce resistance to the hemopoietic effects of recombinant human erythropoietin (rHuEPO) in both rats and dialysis patients (Drüeke, T.B., 1990; Losekann, A. et al., 1990). Therefore, dialysis patients with an obvious aluminum overload may need larger doses of rHuEPO to overcome this resistance, which significantly increases the cost of patient care.

2.2.4 Hypercalcemia

Aluminum-related bone disease may cause hypercalcemia (Norris, K.C. et al., 1985). In a rat study, aluminum changed the relationships between serum PTH, calcium, and phosphorus (Felsenfeld, A.J. et al., 1993). In a study of 25 patients on continuous ambulatory peritoneal dialysis (Cannata, J.B. et al., 1983b) who had accidentally been exposed to high level of aluminum in the dialysate for a month, serum calcium levels significantly increased from 2.27 to 2.44 mmol/L, while serum PTH levels declined from 744 to 580 ng/L. In another study of hemodialysis patients (Cannata, J.B. et al., 1983c), a high serum aluminum level was strongly associated with hypercalcemia and low serum PTH level. Therefore, the suspicion of aluminum overload should be kept in mind in the patient who does not have obvious elevations in serum intact PTH (e.g., less than 500 pg/mL) or who is not taking vitamin D therapy (NKF, 2003).

2.3 Screening and diagnosis for aluminum overload

A histological examination of bone biopsy specimens is still considered the gold standard for diagnosing dialysis patients with an aluminum overload. Biopsies, however, are invasive and expensive. Therefore, several studies have reported their efforts to develop less invasive diagnostic methods of diagnosing aluminum overload (Milliner, D.S. et al., 1984). Serum aluminum measurements are of limited value due to its high tissue accumulation. However, aluminum overload is unlikely in dialysis patients with baseline serum aluminum concentrations (without desferrioxamine (DFO) "stimulation") less than 20 µg/L (NKF, 2003). In one study, 50 dialysis patients undergoing bone biopsy seemed distinguishable, after a DFO

infusion test, from those with a positive bone aluminum stain by an increase in serum aluminum and a relatively high serum iPTH level (McCarthy, J.T. et al., 1990). In another prospective study of 445 dialysis patients to evaluate noninvasive tests that combined the results of intact parathyroid hormone (iPTH) and DFO tests (Pei, Y. et al., 1992), the test were useful for predicting aluminum-related bone disease in dialysis patients using aluminum-based binders. However, they yielded a high incidence of false-negatives and low-sensitivity results after these patients had discontinued aluminum-based binders for more than 6 months. According to the present consensus, the DFO test affords a non-invasive method to identify patients with an increased body burden of aluminum (NKF, 2003) (Evaluation of aluminum-related disorders: considerations for DFO test and subsequent DFO treatment, http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Algorithm7L.jpg).

2.4 Treatment

In addition to dialysis modalities, the K/DOQI guideline (NKF, 2003) also recommends DFO to treat dialysis patients with an aluminum overload. However, DFO has side effects of its own (Cronin, R.E. & Henrich, W.L., 2006), such as itchy skin, nausea, myalgia, and neurotoxicity (McCauley, J. & Sorkin, M.I., 1989). Although most of these side effects are mild and reversible, some rare and severe or even life-threatening side effects are possible, especially anaphylactic shock and mucormycosis (Boelaert, J.R. et al., 1991, 1993). Because of the common side effects of DFO, doses of 20-40 mg/kg of body weight (Bene, C. et al., 1989; Cases, A. et al., 1988; Pengloan, J. et al., 1987) have been abandoned. The toxicity of DFO is dose-dependent; thus, many studies (Barata, J.D. et al., 1996; D'Haese, P.C. et al., 1995; Janssen, M.J. & van Boven, W.P., 1996) were designed to find the optimal dose for aluminum overload treatment. According to the K/DOQI clinical practice guideline (NKF, 2003), the DFO standard dose is 5 mg/kg of body weight (DFO treatment, http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Algorithm9L.jpg). Furthermore, several pharmacokinetic and small-scale, short-term studies (Canteros, A. et al., 1998; Jorge, C. et al., 1999) found that even doses lower than 5 mg/kg were as efficacious as the standard 5 mg/kg dose, but clinical trials verifying its efficacy at lower doses are lacking. Therefore, we compared the response to 2 months of treatment with the standard dose (5 mg/kg) versus a lower dose (2.5 mg/kg) of DFO in dialysis patients with aluminum overload. Both treatment groups showed similar therapeutic effects, there were relatively fewer side effects in the 2.5-mg/kg group (Kan, W.C. et al., 2010).

3. Managing aluminum overload in dialysis patients with hyperparathyroidism

In patients with hyperparathyroidism, calcium-based phosphate binders are always unsuitable because of the frequently associated symptoms of hypercalcemia. Therefore, aluminum-based binders were used, which created a high risk of aluminum overload. Because PTH can protect against aluminum deposition at the mineralization front, perhaps by increasing bone turnover (Slatopolsky, E., 1987), the symptoms of aluminum-related bone diseases may be "masked" in dialysis patients with hyperparathyroidism. However, this "protection" will disappear in patients who have undergone a parathyroidectomy (PTX), because lowered PTH levels will accelerate bone aluminum deposition (Slatopolsky, E., 1987). Therefore, it is generally suggested that aluminum bone disease be excluded before PTX. Similarly, medical treatment of hyperparathyroidism with active Vitamin D₃ (calcitriol) also may accelerate aluminum bone disease. In addition, the risk of aluminum bone disease is greater in diabetics (Andress, D.L. et

al., 1987; Pei, Y. et al., 1993), which may be related to a lower bone turnover rate, which has been reported in type 1 diabetics before the onset of clinical renal disease (Andress, D.L. et al., 1987; Vincenti, F. et al., 1984). Therefore, because of the sometimes similar clinical manifestations of hyperparathyroidism and aluminum overload, physicians treating dialysis patients with hyperparathyroidism should consider the possibility of concurrent aluminum problems, especially in high-risk diabetic patients.

The side effects of DFO are dose-dependent and potentially life-threatening. Although the standard dose for aluminum overload is 5 mg/kg/week for a total of 8 weeks, there are still reports of fatal mucormycosis on such a regimen (Petrikos, G. & Drogari-Apiranthitou, M., 2011). A lower dose of DFO, if it offers good efficacy with fewer side effects, may be promising for managing such complicated patients (Kan, W.C. et al., 2010).

4. Conclusion

Although the prevalence of aluminum overload in dialysis patients is decreasing, it is still an insidious problem worldwide, especially in these dialysis patients still often exposed to aluminum-containing medications. In these patients with hyperparathyroidism, calcium- and aluminum-based binders are not suitable for long-term use (particularly for patients on concurrent vitamin D therapy). Therefore, in these particular patients, especially those with a history of aluminum-containing medications or water exposure, possible concurrent aluminum overload should be kept in mind before medical or surgical intervention. Otherwise, aluminum-related bone disease will be aggravated after treatments. Therefore, several non-calcium, non-aluminum phosphate binders (such as sevelamer hydrochloride and lanthanum carbonate) are suggested despite the high cost and consequent unpopularity of these newly developed medications.

5. Acknowledgment

Sincerely thankful to Miss Hui-Li Hsiao, the Matron of the Dialysis Center in Chi-Mei Medical Center, and all the staff nurses, whose full support and encouragement enabled us to complete the related studies.

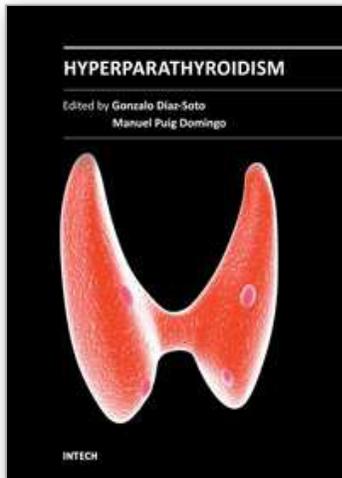
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Hyperparathyroidism

Edited by Dr. Gonzalo Diaz Soto

ISBN 978-953-51-0478-0

Hard cover, 96 pages

Publisher InTech

Published online 04, April, 2012

Published in print edition April, 2012

This book is the result of the collaboration between worldwide authorities of different specialties in hyperparathyroidism. It aims to provide a general but deep view of primary/secondary and tertiary hyperparathyroidism, from a physiological basis to hyperparathyroidism in hemodialyzed patients, as well as new treatment approaches, techniques and surgical scenarios. We hope that the medical and paramedical researchers will find this book helpful and stimulating. We look forward to sharing knowledge of hyperparathyroidism with a wider audience.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Wei-Chih Kan, Chih-Chiang Chien, Yi-Hua Lu, Jyh-Chang Hwang, Shih-Bin Su and Hsien-Yi Wang (2012). Aluminum Overload: An Easily-Ignored Problem in Dialysis Patients with Hyperparathyroidism, Hyperparathyroidism, Dr. Gonzalo Diaz Soto (Ed.), ISBN: 978-953-51-0478-0, InTech, Available from: <http://www.intechopen.com/books/hyperparathyroidism/aluminum-overload-an-easily-ignored-problem-in-dialysis-patients-with-hyperparathyroidism>

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