

Acute Aluminum Neurotoxicity Secondary To Treatment Of Severe Hyperphosphatemia Of Acute Renal Failure And The K/DOQI Guidelines: A Case Report And Review Of The Literature

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Citation

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Abstract

Despite the efficacy of aluminum based compounds to bind phosphate from the gastrointestinal tract in the treatment of hyperphosphatemia associated with renal failure, their use is limited by their potential for multi-system toxicity. The current K/DOQI guidelines recommend their use be limited, both in terms of their indications for use as well as duration of therapy, to prevent the development of such side effects.

We report a case of a patient with renal failure after orthotopic liver transplantation that developed acute encephalopathy from aluminum intoxication following aluminum hydroxide phosphate binder therapy despite its use being limited and within the guidelines set by the current K/DOQI recommendations.

We propose an even more cautious use of these agents and a proactive approach to neurological complications arising amongst patients on this therapy.

INTRODUCTION

Despite the efficacy of aluminum based compounds to bind phosphate from the gastrointestinal tract in the treatment of hyperphosphatemia associated with renal failure, their use is limited by their potential for multi-system toxicity. The current United States Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) guidelines updated in 2004 recommend their use be limited, both in terms of their indications as well as duration of therapy, to prevent the development of such side effects[1].

We report a case of a patient with renal failure after orthotopic liver transplantation that developed acute encephalopathy from aluminum intoxication following aluminum hydroxide phosphate binder therapy despite its use being limited and within the guidelines set by the current K/DOQI recommendations.

We propose an even more cautious use of these agents and a

proactive approach to neurological complications arising amongst patients on this therapy.

CASE REPORT

A 50 yr old white male was admitted via the emergency department of our hospital in July 2004 with an acute decompensation of liver function secondary to recurrent Hepatitis C in an allograft received 8 years earlier. An expedited work-up resulted in a successful re-transplantation 2 days later but the immediate postoperative period was complicated by the development of acute anuric renal failure and severe hyperphosphatemia (see table). His renal failure was thought to be from acute tubular necrosis for which supportive therapies were instituted. Within 24hours he became non-oliguric, and his serum creatinine peaked at 5.3mg/dL (468.5mmol/L) so that he never required dialysis. However, his hyperphosphatemia worsened further and peaked at 12.2 mg/dl (3.94mmol/L). Nephrological consultation on the 3rd postoperative day recommended a

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time and dose limited trial of aluminum hydroxide (Amphogel ® USA) at 45 ml orally thrice a day for a maximum period of 4 weeks. His nasogastric tube feeds were modified to a low Phosphate formulation (Nepro ® USA). By the 9th postoperative day, his Amphogel dose was reduced to 20 ml thrice a day in view of improving renal function and serum phosphate level.

Figure 1

Table 1: Postoperative biochemical parameters

	Na+ Mmol/L	K+ Mmol/L	Cr Mg/dl	Ca+ Mg/dl	Phos Mg/dl	Al Ng/ml	I-PTH Pg/ml
Post-op Day 2	141	4.8	2.8	7.9	7.4	ND	ND
Post-op Day 3	141	5.6	5.3	8.1	12.2	ND	ND
Post-op Day 10	150	4.0	2.4	8.0	8.8	35	ND
Post-op Day 30	139	4.1	1.1	9.9	3.4	ND	28.9
Post-op Day 60	144	4.4	0.9	8.6	2.1	2	27

ND- not determined, I-PTH- Intact parathyroid hormone
To convert serum creatinine in mg/dL to µmol/L, multiply by 88.4
To convert serum calcium in mg/dL to mmol/L, multiply by 0.25
To convert serum phosphorus in mg/dl to mmol/L, multiply by 0.323

On the 10th postoperative day, the patient became confused and delirious with tremors, hallucinations, slurred speech and disorientation. A neuropsychiatric evaluation was obtained. In addition to changing his immunosuppressive regimen and obtaining a serum aluminum level, extensive metabolic and neurological investigation failed to reveal a cause of his neurologic abnormalities. The patient continued to remain in non-oliguric acute renal failure and never required dialytic therapy. On the 33rd post operative day, the results of the serum aluminum level came back at 35ng/ml (normal <2ng/ml). His aluminum based phosphate binder was stopped and a review of his medications failed to reveal concomitant administration of a citrate-containing compound during this period.

The decision to treat his aluminum intoxication with deferoxamine was not pursued in view of a concurrent infection (ventilator associated pneumonia), heart failure, and pharmacological immunosuppression for his allograft. Additionally, his steadily improving renal function (see table) and excellent urine output, was felt to contribute significantly to his body aluminum clearance. His neurologic dysfunction resolved spontaneously and a repeat aluminum level 60 days post transplant was 2 ng/ml.

DISCUSSION

Aluminum neurotoxicity has been classically described as occurring in patients with end stage renal disease receiving

hemodialysis with dialysate containing unacceptably high levels of aluminum, or in the primary management of hyperphosphatemia with aluminum containing compounds. The typical presentation is one of a chronic dementia^[2, 3] usually associated with varying degrees of anemia^[2, 4] that is resistant to erythropoietin and osteodystrophy^[5,6,7] unrelated to secondary hyperparathyroidism. Following the recognition of this clinical syndrome and its etiological basis, strict water treatment policies and abandonment of aluminum phosphate binders has made aluminum neurotoxicity a clinical rarity.

Aluminum containing phosphate binders are still the most potent binders available for varying degrees of gastrointestinal pH_s. For this reason the short term use of these compounds in cases of severe hyperphosphatemia is still practiced occasionally. The updated 2004 K/DOQI guidelines, while approving the use of these agents in dialysis patients and patients with less severe renal impairment, in recognition of the potential for toxicity recommend its use only in patients with serum phosphorus levels >7.0 mg/dL (2.26 mmol/L)^[1]. In such instances, aluminum-based phosphate binders is recommended to be used as a short-term therapy (<4 weeks), and for one course only, to be replaced thereafter by other phosphate binders or more frequent dialysis. The potential for toxicity is increased with concomitant administration of citrate containing medication^[9, 10]. Also several medications contain significant amounts of aluminum that over a prolonged period of time provide a large aluminum load. Drugs like sucralfate or aluminum/magnesium hydroxide products like Mylanta ® (100mg of elemental aluminum/300mg of compound) and Maalox ® (76mg of elemental aluminum/225mg of compound) contain similar amounts of elemental aluminum compared to other aluminum hydroxide products like Alternagel ® (108 mg per 320mg of compound), Basojel ® (108mg per 320mg of compound) or Amphogel ® (100mg per 300mg of compound). Our patient received a tapered dose of an aluminum based phosphate binder for four weeks. However, he began manifesting complications related to this medication as early as 10 days after the start of Amphogel ® and the slow turnover of the serum aluminum test unfortunately allowed continued exposure of the patient to the drug.

Aluminum neurotoxicity can present acutely over a period of days to weeks, subacutely or insidiously over a period of months to years^[11,12,13,14]. This appears to be related to the

dysfunction caused by accumulation of aluminum in the gray matter of the brain^[15]. A wide range of abnormalities including speech defects, agitation, myoclonic jerks, asterexis, defective spatial orientation, altered consciousness and motor seizures have been described^[3]. In advanced cases coma and death have been described^[16]. The electroencephalographic (EEG) findings differ from the generalized slowing noted with other causes of metabolic encephalopathy^[15] with a characteristic pattern of a slow background with superimposed bursts of high-amplitude slow waves, sharp waves, and complexes of spikes and slow waves. The diagnosis rests on a high index of clinical suspicion, EEG features, exclusion of commoner causes of an altered mental status along and confirmation from elevated plasma aluminum levels.

Acute aluminum neurotoxicity is less well described. The commonest clinical scenario described in case reports, have been in patients with varying degrees of renal insufficiency treated with aluminum containing substances^[10, 17, 18, 19]. The most common indication for use of these medications was hyperphosphatemia ^[10, 17]. Cases of acute intoxication have been associated with breaks in the quality of dialysate feed water ^[18]. Other cases involve the use of alum bladder irrigation to treat hemorrhagic cystitis from radiotherapy ^[15, 20].

The serum concentrations of aluminum associated with acute intoxication are usually significantly lower than those described in chronic aluminum toxicity. Acute neurotoxicity manifests at levels of ranging from 14-47 ng/mL ^[10, 17, 18, 19, 20] while chronic neurotoxicity is associated with levels above 100ng/ml^[14, 21, 22, 23]. This strongly suggests that the brain's ability to handle acute elevations of aluminum is more limited than chronic low-grade exposure as is seen in long-term dialysis patients. Unlike the progressive dementia of chronic aluminum neurotoxicity, the symptoms of acute aluminum neurotoxicity are reversible and positively correlate with serum levels,^[19] as was the case with our patient.

The natural history of aluminum excretion has not been characterized in great detail. Aluminum is 90% protein bound (primarily to transferrin) and has a wide volume of distribution in body tissues like the bone, brain, muscle, heart, lungs, parathyroids and other organs^[12, 13, 15]. Aluminum is eliminated in the urine and bile and in intoxicated patients the kidney is the major route of

elimination ^[15]. These pharmacokinetic properties make dialysis alone ineffective in clearance of aluminum. Renal handling of aluminum seems to be an interplay of glomerular filtration and tubular reabsorption. One review of aluminum excretion in dialysis patients within the first 90 days post renal transplant, described maximal fractional excretion of aluminum during periods of sub optimal serum creatinine and allograft tubular injury^[24]. The fractional excretion fell slightly but significantly with resolution of tubular injury. Another study described near normalization in bone morphometric parameters in renal transplant recipients at 1 year post transplant^[25]. This suggests that the excretion of aluminum and removal from excess body stores could take more than a year and is dependent on the total body burden of aluminum and renal function.

TREATMENT

Deferoxamine is a well known polyvalent cation chelator that has proven effective in decreasing total body aluminum burden in chronically intoxicated dialysis patients ^[26, 27]. Upon administration, it forms an aluminum-deferoxamine complex called aluminoxamine with a molecular weight of about 600 daltons and elimination half-life of about 2-4 hours. The excretion of this complex is dependent on clearance by the kidneys of elimination during dialysis. The affinity of deferoxamine for aluminum is marginal and its dissociation in serum can increase aluminum levels in serum unless rapidly cleared by urinary excretion or dialysis^[15]. Administered intravenously or intraperitoneally, it can be used in both hemodialysis and peritoneal dialysis patients with notable clearance in peritoneal dialysate and modern day high flux hemodialysers^[27, 28].

The recommended dose of deferoxamine in the management of this condition is between 5-20 mg/kg body weight. The higher doses during clinical trials and analysis of an international registry of dialysis patients confirmed a higher risk of adverse effects including anaphylactic shock, blindness, and infections such as mucormycosis, yersiniasis and salmonellosis ^[27, 28, 29]. For aluminum neurotoxicity, weekly low dose deferoxamine at 5mg/kg body weight followed by dialysis 6-8 hours after administration of the drug has been associated with the lowest side effect profile ^[15, 27]. The above mentioned method has also been used as a diagnostic test for chronic aluminum overload. Aluminum levels determined 2-4 hours after administration of deferoxamine show a 5-10 fold increase, suggesting mobilization of body stores of aluminum^[21].

The potentially devastating infections and other adverse effects associated with the use of deferoxamine make its use in immunosuppressed patients like ours a cause for concern. While the decision was made not to use the drug for our patient in view of transplant related immunosuppression there has been one report of successful use in a pediatric patient on chemotherapy for acute lymphoblastic leukemia for nine weeks at low doses to augment urinary aluminum excretion^[19].

CONCLUSION

In conclusion, hyperphosphatemia is a common complication of acute renal failure and may warrant the use of potent aluminum based phosphate binders for a short period. However, despite adhering to the stipulations suggested by the K/DOQI guidelines to limit its use to less than 4 weeks, acute neurotoxicity can develop in patients with renal failure within 10 days as seen in the case we describe. They should not be first line agents for addressing this condition except for the most severe cases. The use of dialysis or non-aluminum based agents should be strongly considered as an alternative to the use of these agents. Aluminum based phosphate binder therapy when utilized should be used for a shorter period of time than currently recommended and should not be repeated. Concomitant use of citrate containing compounds potentiates aluminum absorption and hence should be avoided. Any subsequent concerns for an altered mental status in these patients should include a timely estimation of serum aluminum level along with exclusion of other more common causes of delirium. Patients with associated severe renal failure benefit from combined treatment with deferoxamine and hemodialysis. In patients with preserved renal function, renal excretion of aluminum is enhanced by deferoxamine administration. The risks of infection and other adverse effects with the use of deferoxamine should be weighed carefully on an individualized basis. Low dose deferoxamine may avert most of these problems.

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