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Assessing the utility of testing aluminum levels in dialysis patients

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Abstract

Plasma aluminum (Al) is routinely tested in many dialysis patients. Aluminum exposure may lead to acute toxicity and levels in excess of ~2.2 μmol/L (60 μg/L) should be avoided. Historically, toxicity has been caused by excessive dialyzate Al but modern reverse osmosis (RO) water should be Al free. Nevertheless, many units continue to perform routine Al levels on dialysis patients. This single-center study retrospectively analyzed Al levels in plasma, raw water feed, and RO product between 2010 and 2013 using our database (Nephworks 6) with the aim of determining the utility of these measurements. Two thousand fifty-eight plasma Al tests in 755 patients (61.9% male, mean age 64.7 years) were reviewed showing mean ± SD of 0.41 ± 0.30 μmol/L. One hundred eleven (5.4%) tests from 61 patients had Al levels >0.74 μmol/L and 45 (73.8%) of these patients were or had been prescribed Al hydroxide ($Al(OH)_3$) as a phosphate binder. Seven patients had Al concentrations >2.2 μmol/L with no source of Al identified in 1 patient. One hundred sixty-six patients taking $Al(OH)_3$ (78.7% of all patients on $Al(OH)_3$) had levels ≤0.74 μmol/L, the odds ratio of plasma Al > 0.74 μmol/L on $Al(OH)_3$ was 9. The cost of plasma Al assay is $A30.60; thus, costs were $A62,974.80 over the study period. Despite RO feed water Al levels as high as 48 μmol/L, Al output from the RO was almost always undetectable (<0.1 μmol/L) with dialyzate Al levels > 2.2 μmol/L only 3 times since 2010, and never in the last 3 years. Routine unselected testing of plasma Al appears unnecessary and expensive and more selective testing in dialysis patients should be considered.

Key words: Aluminum, chronic kidney disease, contamination, dialysis, hemodialysis, phosphate binders

INTRODUCTION

Aluminum (Al) is cleared from the blood exclusively by glomerular filtration. Thus, patients with renal failure accumulate Al and are the only routine patient group likely to be at risk of Al toxicity. Al overload results in accumulation principally in the skeleton and the brain and manifests with osteomalacia (resistant to vitamin D therapy), bone and muscle pain, iron-resistant microcytic anemia, and neurologic abnormalities including speech disorders, encephalopathy and dementia.[1]

Acute Al toxicity is rare, and mostly related to Al phosphide (AlP), which is used as a pesticide. Exposure to water or ingestion of AlP causes the release of the highly toxic phosphine (PH_3) leading to rapid free radical injury, circulatory collapse, and death.[2] The Al per se only seems to be an issue if given concurrently with sodium citrate

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which dramatically increases Al uptake, and in dialysis patients this leads to very high plasma levels ~2000 μg/L (~75 μmol/L) which can result in potentially fatal neurological toxicity.[3]

Most of the early occurrence of chronic Al toxicity was reported between 1965 and mid-1980s and primarily caused by excessive Al in dialyzate water in patients undergoing chronic hemodialysis (HD) therapy,[4] but it has also been reported after contaminated peritoneal dialysis (PD) fluid.[5] In the early days of dialysis, the preparation of dialyzate water was unsophisticated and subject to contamination from a number of sources, including the addition of Al as a flocculant to remove colloidal matter. Moreover, water purification often involved using stainless steel boilers, sometimes fitted with Al-based cathodic corrosion protection systems, leading to high Al levels in the dialyzate. Modern water preparation using reverse osmosis (RO) membrane systems, reduction in the use of Al-based phosphate binders, and the avoidance of calcium citrate means that acute or chronic Al toxicity is rarely (if ever) encountered in modern practice.[6] Al-based phosphate binders are now infrequently prescribed across the world, but apparently more in Australia/New Zealand.[6] Thus, Al-based binders[6] and Al-containing antacids now represent the major source of Al exposure in patients with end-stage kidney disease (ESKD). Aluminum can also be a contaminant present in oral and injectable medications as part of the manufacturing process,[7,8] in particular albumin products. Albumin binds Al during the purification process when passed through Al silicate filters, and thus long-term use of i.v./blood products is another potential source of excess Al.[9] There have also been reports of sepsis causing release of Al from tissue stores.[10]

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for the care of patients with ESKD recommended screening for Al toxicity with Al concentrations at least yearly, and quarterly in those receiving Al-containing medications; however, these were outlined in the guidelines as opinion-based recommendations.[11] The more recent international Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD) guidelines recommend avoiding long-term use of Al-containing phosphate binders and, in patients with ESKD on dialysis, dialyzate Al decontamination to prevent Al intoxication.[12] However, there are no KDIGO recommendations regarding measurement of plasma Al levels. There appears to be a low incidence of high Al levels among current dialysis patients[13] with no reported outbreaks of Al toxicity in recent literature except sporadic clusters of cases of elevated Al levels.[14]

There have only been a few retrospective studies published evaluating the frequency of abnormal plasma Al levels, the predictive value of Al testing, cut-off levels for toxicity, and the utility of routine screening in an era of Al-free dialyzate water and decreased Al-based binder administration.[13,15–17] Some investigators have advocated reevaluating the safety of Al-based phosphate binders given low demonstrated risk of toxicity and a cost benefit over contemporary first-line phosphate binders although prospective trials are lacking.[6,18]

In light of the reduction in exposure of dialysis patients to Al, an audit at our institution was undertaken to assess the requirements for continued monitoring of patients and the water quality of dialyzate. We report a single-center study assessing the frequency of abnormal Al levels in a cohort of dialysis patients over a period of 4 years with the aim of evaluating the clinical benefit of routine Al measurement.

METHODS

We performed a retrospective cohort study of dialysis patients at The Royal Melbourne Hospital (RMH), Parkville, Australia. All dialysis patients undergo routine annual surveillance of plasma Al concentrations at RMH, with biannual measurements for patients prescribed Al-based phosphate binders. We retrospectively retrieved all plasma Al levels tested for the dialysis population from January 2010 to December 2013 using our computerized nephrology database (Nephworks 6), as well as RO and water feed Al levels on all HD patients. Nephworks contains prospectively documented patient history, medications, comorbid events, and outcomes for all dialysis patients at RMH. Medical records of patients with abnormal plasma Al levels were reviewed to determine Al exposure.

Laboratory methods

Five milliliters of blood was collected into K_2-EDTA anticoagulated BD Vacutainer® (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) Blood Collection Tubes for Trace Element Testing. This avoids significant contamination (20–60 ug/L) by the rubber stoppers made from Al silicate that are commonly used in standard evacuated blood tubes.[19] The sampling needle is not usually a problem for Al.

Plasma Al levels were measured using dual beam graphite furnace atomic absorption spectrophotometry with an AAnalyst 800 spectrophotometer (Perkin Elmer, Waltham, MA, USA) throughout the study period. The lab cut-off value for plasma Al was <0.8 μmol/L with a local

range between 1.5 and 2.0 μmol/L for patients with ESKD on Al-based binders. There is no well-defined threshold level of plasma Al concentration indicating toxicity in dialysis patients.[20] Previous studies have used different cut-off levels including 0.74 μmol/L (20 μg/L), 1.48 μmol/L (40 μg/L), 2.22 μmol/L (60 μg/L), and 3.0 μmol/L based on varying evidence and local lab parameters.[13,16–18] KDOQI guidelines recommend Al levels to be tested quarterly and be less than 0.74 μmol/L with the use of the deferoxamine (DFO) mobilization test[21] for elevated levels between 2.22 and 7.42 μmol/L (60–200 μg/L, respectively).[11] In our study, we used a cut-off value of >0.74 μmol/L to indicate abnormal levels and ≥2.2 μmol/L to indicate risk of toxicity for analysis.

We routinely undertake trace element analysis in dialyzate water collected from various sites across multiple dialysis centers. Mains water and RO output is regularly tested for Al by our service.[22] There are suggested limits of <100 μg/L (3.71 μmol/L) for large processing plants and <200 μg/L (7.42 μmol/L) for smaller plants serving 10,000 people or less.[23] We reference American National Standard ANSI/AAMI RD62:2006, which indicates maximum allowable concentration of Al in "water used to prepare dialyzate" as <10 ug/L (<0.37 μmol) for our dialysis network. We also reviewed Al levels in the dialyzate water source over this period as there are guidelines for drinking water Al content suggested by the World Health Organization (WHO).

Statistics

This is predominantly a descriptive study. Descriptive statistics are presented as mean (± standard deviation) or percentages. Data analyses were performed on individual plasma Al concentrations and not based on the mean plasma Al level per patient. Therefore, both the number of Al determinations and the number of patients are given. Mann–Whitney *U*-test was used to determine differences between patients taking and not taking Al-based phosphate binders according to Al levels. Logistic regression was used to compare differences in Al levels and Al hydroxide ($Al(OH)_3$) use over time. Stata statistical software package (version 11.0, Stata Corporation, College Station, TX, USA) was used for analysis.

RESULTS

We retrieved a total of 2058 plasma Al measurements for 755 patients over the 4-year period. The dialysis cohort had a mean age of 64 years and 62% were male (Table 1). The mean plasma Al level was 0.41 ± 0.30 μmol/L (11 ± 8.08 ug/L). A total of 211 of these patients were or had been prescribed $Al(OH)_3$ as an oral phosphate binder. Of 2058 measurements, 111 (5.4%) tests from 61 patients had Al levels greater than 0.74 μmol/L with 45 (73.8%) being on $Al(OH)_3$. These 61 patients included 47 on HD, 6 on PD, and 8 on home HD. Ten results (0.49%) were equal to or greater than 2.2 μmol/L in 7 patients out of which 6 had been prescribed $Al(OH)_3$, with no source of Al identified in 1 patient who was undergoing dialysis at home at the time and returned normal Al level on repeat testing. There was no evidence of clinical toxicity due to elevated Al levels on review of the available medical records for these patients. One hundred sixty-six patients taking $Al(OH)_3$ (78.7% of all patients on $Al(OH)_3$) had levels ≤0.74 μmol/L. The odds ratio of plasma Al > 0.74 μmol/L on $Al(OH)_3$ was 9.

$Al(OH)_3$ as a potential source of abnormal levels was identified in 45 of 61 patients (Table 2), although the cumulative Al load in patients on $Al(OH)_3$ could not be calculated given inconsistent information available regarding the dose of binders administered. In the remaining 16 patients, the abnormal results were presumed to be erroneous or a result of inadvertent exposure to Al through equipment or medications based on the lack of repeated elevated levels, levels in the nontoxic range (93.7%), and a tendency to revert to normal on repeat testing. On follow-up tests, the levels reverted to or trended toward

Table 1 Patient characteristics for all dialysis patients

Characteristics	N = 755 (%)
Age (years)[a]	63.2 ± 14.9
Gender	
Male	467 (61.9)
Female	288 (38.2)
Cause of ESKD	
DM	197 (26.1)
GN	200 (26.5)
HT	59 (7.8)
PCKD	55 (7.3)
Reflux	39 (5.2)
Other (and unknown)	205 (27.1)
Dialysis modality	
HD	582 (77.0)
PD	119 (15.8)
HHD	54 (7.2)
Duration on dialysis (mo, median [IQR])[a]	32 (61.5-9.9)

[a]At the time of the last Al level.
DM = diabetes mellitus; GN = glomerulonephritis; HD = hemodialysis; HHD = home hemodialysis; HT = hypertension; PCKD = polycystic kidney disease; PD = peritoneal dialysis; Reflux = reflux nephropathy.

Table 2 Number of patients with normal and abnormal plasma aluminum levels in relation to administration of aluminum-based phosphate binders

Al level (μmol/L)	N = 755	No $Al(OH)_3$ N = 544 (%)	$Al(OH)_3$ N = 211 (%)	P value*
<0.74	694 (91.9%)	528 (97.1%)	166 (78.7%)	<0.01
0.74–2.1	54 (7.2%)	15 (2.8%)	39 (18.5%)	<0.01
≥2.2	7 (0.9%)	1 (0.2%)	6 (2.8%)	0.01

Al = aluminum; $Al(OH)_3$ = aluminum hydroxide.
*P value for significance between subjects taking vs. not taking $Al(OH)_3$ for various Al concentrations.

normal in 47 of 61 patients (77%, including 12 patients not on $Al(OH)_3$) with Al levels >0.74 μmol/L. Out of 7 patients with Al > 2.2 μmol/L, only 1 patient had multiple elevated levels, with maximum of 3.64 μmol/L, which reverted back to normal on cessation of $Al(OH)_3$. None of the patients had Al level >7.4 μmol/L.

Al levels measured in the dialyzate water precluded any risk of exposure from that source. Despite RO feed water Al levels as high as 48 μmol/L (1300 ng/mL), Al output from the RO was almost always undetectable (<0.1 μmol/L). We have detected dialyzate Al levels >2.2 μmol/L only 3 times since January 2010, and never in the last 3 years.

The frequency of elevated plasma Al levels (>0.74 μmol/L) in patients on dialysis declined each year from 8.72% in 2010 to 2.35% in 2013, perhaps related to declining use of Al-based phosphate binders. Administration of $Al(OH)_3$ in subjects in this study declined from 31.7% to 4.75% over the same period (Table 3). The cost of single plasma Al assay is $A30.60 resulting in the total cost over the study period of $A62,974.80, or amounting to over $A1300 per month.

DISCUSSION

Al toxicity has been known to cause serious complications although the incidence of cases in the current dialysis population is very low given the elimination of Al from dialyzate water and the decreased use of Al-based phosphate binders. As we have continued to routinely measure plasma Al levels on all dialysis patients at our local center, we performed a retrospective observational study to determine the frequency of abnormal Al concentrations and assess for associations with any clinical history of toxicity, use of Al-based binders, and cost of routine measurements. We report a very low number of elevated Al levels in 755 patients over a 4-year period.

Al is ubiquitous in nature with only a tiny fraction of ingested Al absorbed and normally excreted by the kidneys. Previously, when Al was added to the dialyzate for patients undertaking HD, it would enter the body directly leading to syndromes of toxicity. However, there has been complete absence of reports of the "dialysis dementia" syndromes formerly attributed to Al toxicity in ESKD, and a substantial reduction in the prevalence of Al-related bone disease, with improvements in the quality of dialyzate water.

Plasma Al levels reflect relatively recent exposure to Al.[24,25] Monitoring Al levels might identify excessive Al intake or absorption in individual patients, aid in the recognition of accidental contamination of dialyzate with Al, and screening may potentially allow earlier recognition of Al loading with greater ability to prevent toxicity.

Table 3 Percentage of abnormal plasma aluminum levels with relationship to patients on aluminum hydroxide according to each year

Year	Patients, N	Patients on $Al(OH)_3$, N (%)*	Plasma Al levels, N	Al > 0.74 μmol/L, N (%)**	Al > 2.2 μmol/L, N (%)
2010	451	143 (31.7)	562	49 (8.7)	5 (0.9)
2011	401	46 (11.5)	524	32 (6.1)	3 (0.6)
2012	420	26 (6.2)	547	20 (3.7)	2 (0.4)
2013	363	18 (4.9)	425	10 (2.4)	0 (0.00)

Al = aluminum; $Al(OH)_3$ = aluminum hydroxide.
*P value < 0.01 for relationship between $Al(OH)_3$ administration over time, **P value < 0.01 for relationship between Al > 0.74 μmol/L over time.

Plasma Al levels, however, are not reliable predictors of chronic Al exposure and there is lack of consensus on threshold cut-off values indicating toxic levels. Historically, routine measurements of plasma Al concentrations have been recommended based on prevalent significant risk of toxicity,[15,26] but later studies have questioned the utility and cost-effectiveness of routine plasma Al measurements in all dialysis patients.[13,16–18] Many dialysis units, however, continue to measure Al levels routinely.

One study reported the incidence of abnormal Al levels in dialysis patients to be as low as 2.1%[13] while another reported an incidence of 4.2%, although the cut-off value of abnormal results in this study was 0.74 μmol/L compared to 1.48 μmol/L in the former.[16] The frequency of abnormal results in our study was 5.4% and 0.49% for results signifying risk of toxicity using the cut-offs of 0.74 and 2.2 μmol/L, respectively. This is consistent with previous studies reflecting an extremely low incidence of abnormal Al levels and greatly reduced risk of toxicity compared to the era of significant Al exposure via dialyzate water and regular use of Al-based phosphate binders.

One study from the United Kingdom argued that measuring Al levels routinely in the current era was unnecessary, although the dialysis patients in that study were not taking any Al-based phosphate binders and Al testing of the dialysis water supply achieved an acceptable minimum safety requirement.[17] Another study reported on the impact of double RO system and continued use of Al phosphate binders in a cohort of dialysis patients between 1998 and 2007.[27] This study reported a reduction in serum Al levels in patients after the new RO with no plasma Al level more than 40 μg/L (1.48 μmol/L), even with Al-based binders.

Plasma Al levels of >3.0 μmol/L have been associated with toxicity; however, defining a baseline plasma Al concentration threshold to diagnose toxic Al accumulation is difficult.[20] There is not a single report in the literature of significant Al toxicity occurring in the presence of Al levels less than 1.5 μmol/L. Elevated Al levels above 1.5 μmol/L in 1 Australian report occurred in less than 2% of patients.[6] Most elevated Al concentrations are one-off isolated levels with sustained abnormal concentrations being uncommon.[16] Therefore, consistent with our study, the literature also supports that the number of elevated Al levels is exceedingly low and often transient. There are no published data to determine whether an increase in plasma levels over time leads to tissue accumulation of Al.

Al replaces calcium at the mineralization front in bone, disturbing osteoid formation and causing low turnover bone problems. There is evidence that single measurements of serum Al show correlation with Al bone disease, with 1 study demonstrating a level greater than 100 μg/L (3.7 μmol/L) as a reliable indicator of Al deposits in bone.[28] Another reported a threefold higher risk for this complication in patients in the highest quartile of serum Al, although there was no threshold level of Al that discriminated between patients with Al bone disease and those without.[15] Another reported that a serum Al level of 60 μg/L (2.22 μmol/L) in combination with an intact Parathyroid Hormone (PTH) < 16 pmol/L provided a relatively sensitive and specific index for the detection of Al-related bone disease.[26]

The diagnosis of Al bone disease is important and some dialysis units continue to monitor Al levels regularly because of concerns that exposure may continue from medications used without knowledge such as over-the-counter antacids. Many other prescribed medications also contain hidden Al in smaller amounts.[6–8,16] One report suggested regular attention should be paid to reviewing medications known to contain significant amounts of Al that patients may be taking without knowledge of their physicians.[16] Al levels have been shown to be higher in patients receiving injectable drugs such as iron, insulin, or erythropoietin compared to those who did not receive these medications.[8]

With the move toward hemodiafiltration and the exposure to even more dialyzate water, there is the potential for increased exposure to Al from poorly maintained or failing RO membranes, so it would be important to maintain review of dialyzate Al and raw water Al levels. The problems associated with Al toxicity are not just confined to HD patients, but patients undertaking PD are also at risk. Al-based phosphate binders have been reported to contribute to toxicity in the latter population as well as non-dialyzed uremic individuals.[29,30]

The possibility of sample contamination due to extraneous sources of Al in samples needs to be considered. Al is a ubiquitous metal and contamination of plasma can occur from sources including environmental dust on the blood tubes or gloves. Considerable care is required in the storage of tubes, phlebotomy procedure, and sample preparation for the determination of Al levels to prevent contamination.

With a very low frequency of elevated total Al levels signifying risk of toxicity (0.49%) at our center and at a significant monetary cost, routine plasma Al determinations in patients at low risk are unlikely to be cost-effective. One report from the United States highlighted that the cost of Al levels may range from $40 to $100 (Spectra Laboratories) and therefore yearly costs of $32,000–$80,000 could be incurred with routine measurement for an average dialysis unit.[16]

Studies have reported that patients on dialysis taking Al-based phosphate binders with RO-treated water had no evidence of Al toxicity, and therefore arguing that the use of Al binders in the era of RO-treated dialysis water may be safe. The vast majority of dialysis patients in our cohort with abnormal plasma Al levels were taking $Al(OH)_3$ as a binder. Although only 21% of all patients on $Al(OH)_3$ had transiently elevated Al levels, this compares to only 3% of subjects not taking Al-based binders. We also report the reduction in use of $Al(OH)_3$ over time with a significantly decreased exposure to these binders being associated with a decreased proportion of patients having elevated Al levels in the more recent period.

Limitations of our study include lack of information on residual renal function, inability to accurately determine the cumulative dose of Al-based binders in individuals, and absence of DFO testing to assess total body Al load. Our study does not address the predictive value of abnormal plasma Al levels and when the frequency of abnormal levels in a population is extremely low, the utility of that test as a screening tool becomes negligible. The other consideration of Al measurement should be of cost-effectiveness, which could not be demonstrated in our study.

Plasma Al as a suitable measure of the body burden to this metal is questionable. Although there is a correlation between plasma levels and Al bone disease, the predictive value of Al concentrations for bone disease is poor. The evidence that Al is absorbed from $Al(OH)_3$ and other Al-containing compounds is indirect, and the methodology for measuring Al levels using stable isotope and mass spectroscopy is very expensive, has limited availability, and should only be performed on a small number of patients. In summary, we feel that regular unselected testing of all dialysis patients is probably unnecessary given the frequency of plasma results indicative of Al overload. The costs of such a testing strategy make it unlikely to be cost-effective. From a patient safety point of view, it makes more sense to monitor RO water levels periodically to ensure the RO is working efficiently. There is some logic in assessing Al levels in patients in whom the risk of overload is high and there is clinical suspicion of toxicity, e.g., those exposed to long-term therapy with Al-containing medications like $Al(OH)_3$, antacids, and concomitant use of any drug that augments gut absorption. Furthermore, guidelines and recommendations should be updated to reflect the reduced risk of exposure from Al-containing dialyzate. Isolated high levels are likely to be caused by contamination at the time of testing and not true Al overload. On the basis of our review, we have now moved to only perform selected testing of plasma Al on the basis of assessment of clinical risk, while routine testing of dialyzate Al is continuing.

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