Aluminum Toxicity

Evaluation of 16-Year Trend Among 14,919 Patients and 45,480 Results

Ron B. Schifman, MD; Daniel R. Luevano, BS

Sustained exposure to aluminum from contaminated water used for dialysis can cause a severe and sometimes fatal encephalopathic disorder.1 A second factor contributing to chronic toxicity in dialysis patients is from ingestion of aluminum-containing binders used to treat hyperphosphatemia due to poor efficiency of dialysis in removing phosphate as well as enhanced uptake of aluminum from the gastrointestinal tract.2 Aluminum toxicity can also lead to iron-refractory microcytic anemia and osteomalacia.3–8 Recognition of these risk factors has led to successful preventative measures including treatment by reverse osmosis to remove aluminum from water used for dialysis along with monitoring its aluminum content. In addition, it is recommended that aluminum-containing phosphate binders or other aluminum-containing medications be avoided in patients undergoing dialysis whenever possible.9,10 Because of these actions, aluminum toxicity in dialysis patients is now uncommon.11–13 Nevertheless, guidelines from the National Kidney Foundation recommend annual serum aluminum testing for ongoing surveillance in patients undergoing chronic dialysis, or more frequently if receiving aluminum-containing medications.9

Aluminum is a ubiquitous ultratrace element, and exogenous sources of this metal may lead to false serum elevations due to contamination during collection, processing, or analysis.14,15 Erroneous elevated results may also be caused by other factors such as mislabeling, reporting, or analytic problems such as problems with solution preparation or instrument malfunctions.16,17 However, the frequency with which any of these potential problems lead to inaccurate serum aluminum measurements is unknown. False elevation in serum aluminum concentrations may cause misinterpretation of results and lead to unnecessary measures to check for sources of exposure, to conduct more intensive environmental testing, or may result in unnecessary treatment. Since serum aluminum measurements are most commonly used to screen asymptomatic dialysis patients with low and decreasing incidence of chronic aluminum toxicity, the proportion of abnormal serum aluminum concentrations associated with analytic and nonanalytic problems would be expected to increase. The objective of this study was to investigate long-term trends in serum aluminum levels in a large veteran population and estimate the frequency of chronic toxicity over time.

Results.—A total of 45,480 serum aluminum results involving 14,919 patients and 119 Veteran Affairs facilities during a 16-year period ending in October 2016 were evaluated. The percentage of elevated (≥20 μg/L) serum aluminum results declined from 31.5% in 2000 to 2.0% in 2015. Average testing intervals changed from every 159 days in 2000 to every 238 days in 2015. Of 529 patients with serum aluminum concentrations of 60 μg/L or greater, 216 (40.8%) were retested within 45 days (average = 21 days); of these, 83 (38.4%) had concentrations below 20 μg/L after repeated measurements. Retesting rates increased with higher initial serum aluminum concentrations.

Conclusions.—Aluminum toxicity, as assessed by serum levels, has substantially declined over time and is now rare. Many serum aluminum concentrations in the toxic range were not confirmed after retesting. Patients with toxic serum aluminum concentrations should be retested with another specimen before undergoing treatment or investigating sources of exposure to verify abnormal results.

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From the Departments of Diagnostics (Dr Schifman) and Pathology and Laboratory Medicine (Mr Luevano), Southern Arizona VA Healthcare System, Tucson; and the Department of Pathology, University of Arizona, Tucson (Dr Schifman).
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Corresponding author: Ron B. Schifman, MD, Southern Arizona VA Healthcare System, 3601 S 6th Ave, Tucson, AZ 85723 (email: ronald.schifman@va.gov).
METHODS

A retrospective observational study was conducted involving all identifiable serum aluminum results obtained from the Veterans Affairs (VA) corporate data warehouse. These data included the date that results were reported and the collecting facility. Owing to the nature of the study design, no patient demographics, clinical information, or methods used for aluminum measurements were obtained. Serum aluminum results that were reported as less than or greater than a specific value were rounded to the next lowest or highest whole number, respectively. For example, a result reported as less than 4 μg/L was converted to 3 μg/L. Serum aluminum concentrations below 20 μg/L were considered normal. The time intervals in which individual patients were retested were calculated as the number of days between aluminum measurements during a rolling 2-year period. An elevated result was presumed to be unrelated to chronic toxicity if measurement of the initial specimen was 60 μg/L or greater followed by another test result within 45 days that was below 20 μg/L. When calculating the rate at which specimens were retested within 45 days at various cutoff levels, the second specimen tested was excluded from the total (denominator). This study was reviewed and approved by the patient privacy and research oversight officials at the authors’ institution.

RESULTS

A total of 45 480 serum aluminum results involving 14 919 patients and 119 VA facilities during a 16-year period ending in October 2016 were evaluated. The distribution of aggregate results by year at various cutoff levels from below 20 μg/L to above 200 μg/L is shown in Table 1. Annual changes over time in the frequency of abnormal serum aluminum results (>20 μg/L) and average retesting interval in days for all cases are shown in the Figure. Many laboratories reported serum aluminum levels intermittently with only a few annual tests throughout the entire study period. The median annual test count per laboratory was 4.2 with 10th to 90th percentile range of 1.0 to 86.3. For this reason, we selected a subgroup of laboratories with the most consistent and highest aluminum testing volumes. Table 2 shows the distribution of serum aluminum concentrations.
observed in 14 facilities in which the aluminum test volume was 18 or more tests per year continuously between 2000 and 2015.

A relatively high rate of abnormal aluminum levels in 2007 was found to be associated with a cluster of 85 results ranging from 60 to 200 μg/L with 4 exceeding 200 μg/L at a single facility. This accounted for 78.8% (89 of 113) of all aluminum results that were 60 μg/L or greater for that year. During 2007, the average aluminum concentration observed at this facility was 85.9 μg/L. Among 124 measurements between January and April, the average aluminum concentration declined to 8.9 μg/L among all 65 results reported after April. When all results (n = 189) from this facility were excluded, the percentage of values that were 60 μg/L or greater for the remaining facilities was 1.0% (24 of 2498) in 2007, which aligned well with the continuous trend in declining serum aluminum levels observed over time.

A similar cluster of 19 elevated serum aluminum levels between 60 and 200 μg/L was identified at a single facility in 2011, which represented 73.1% of 26 cases with results within that range among all facilities that year. A total of 10 of 19 patients (52.6%) within this subgroup were retested within 16 to 34 (median = 18) days, of which 9 (90.0%) had concentrations below 20 μg/L while the other had declining concentrations from 73 to 22 μg/L after 16 days. This cluster accounted for the transitory break in downward trend of toxic aluminum cases during 2011 (Table 1).

Table 3 shows the frequency of 3035 testing episodes in which measurements were repeated on another specimen from the same patient within 45 days, stratified by range of initial results from below 20 μg/L to above 200 μg/L. The average retesting interval was 19 days. Higher initial serum aluminum concentrations were associated with more frequent retesting. Among the 216 cases in which the initial serum aluminum level was 60 μg/L or greater, the repeated value was below 20 μg/L in 83 (38.4%). In this group, the average retesting interval was 21 days. A subgroup (not shown in Table 3) of 951 cases for which measurements were repeated within 7 days included 29 cases with initial results that were 60 μg/L or greater, of which 13 (44.8%) were less than 20 μg/L when retested.

**DISCUSSION**

Preventive measures for reducing aluminum toxicity in dialysis patients have been largely successful as borne out by previous studies showing a steady decline in average serum aluminum concentrations over time. For example, one report involving nearly 350 000 aluminum levels among a nationwide dialysis provider found a substantial decline in abnormal (>50 μg/L) serum aluminum concentrations from 3.5% in 2000 to 0.8% in 2002. Another retrospective study in hemodialysis patients, covering an 8-year period (2002–2009), reported serum aluminum concentrations greater than 20 μg/mL in 32 of 5674 specimens (0.5%). The present study involves a longer period than others and of note is that the trend in frequency of elevated serum aluminum concentrations has continued to decline without, as of 2016, yet leveling off.

Guidelines from the National Kidney Foundation, issued in 2003, recommended annual screening for asymptomatic patients undergoing dialysis who do not have other risk factors (eg, medications) for aluminum toxicity. Nevertheless, as shown in the Figure, the frequency of testing began to decline in 2009, suggesting a delayed adoption of these recommendations. However, testing is still more frequent (about 1.5 times per year) than what might be expected from recommendations for annual testing. Further, testing intervals have remained relatively constant since 2011 despite a declining overall rate in abnormal serum aluminum levels. The reason why testing frequency has not continued to decline is unknown but may be related to local ordering practices and systems established for maintaining and tracking testing schedules. It should also be noted that this study was not designed to determine how many dialysis patients were not regularly tested at all for serum aluminum, which may be more common now that risk of toxicity is so low.

Owing to the infrequent incidence of abnormal aluminum results in dialysis patients, as shown in this study and others, some have advocated eliminating routine annual

**Table 2. Range of Aluminum Concentrations by Facility (N = 14)**

| Year | Median Test Volume per Facility | Serum Aluminum (μg/L) Median (25th–75th Percentile) |
|------|--------------------------------|---------------------------------------------------|
| 2000 | 69                             | 17.6 (13.7–20.2)                                  |
| 2001 | 75                             | 16.7 (12.2–17.9)                                  |
| 2002 | 65                             | 14.9 (11.1–16.7)                                  |
| 2003 | 68                             | 11.3 (10.4–12.9)                                  |
| 2004 | 62                             | 11.9 (7.9–13.9)                                   |
| 2005 | 62                             | 11.2 (9.1–13.2)                                   |
| 2006 | 63                             | 11.3 (9.8–14.1)                                   |
| 2007 | 67                             | 10.6 (9.3–13.1)                                   |
| 2008 | 71                             | 9.6 (7.8–10.5)                                    |
| 2009 | 70                             | 9.9 (8.4–11.4)                                    |
| 2010 | 64                             | 11.1 (10.4–13.1)                                  |
| 2011 | 88                             | 12.7 (10.1–14.2)                                  |
| 2012 | 60                             | 9.2 (8.1–10.2)                                    |
| 2013 | 49                             | 7.4 (6.2–8.8)                                     |
| 2014 | 53                             | 7.4 (6.1–11.3)                                    |
| 2015 | 55                             | 7.9 (5.7–9.0)                                     |

**Table 3. Results From Specimens Retested Within 45 Days**

| Initial Results, μg/L | Total | Retested, No. (%) | Results (μg/L) From Repeated Measurements Within 45 Days, No. (%) |
|-----------------------|-------|-------------------|---------------------------------------------------------------|
|                       |       |                   | <20  | 20–39 | 40–59 | 60–200 | >200 |
| <20                   | 36 369| 2108 (5.8)        | 1851 | 219   | 19    | 18     | 1    |
| 20–39                 | 4733  | 554 (11.7)        | 269  | 216   | 48    | 21     | 0    |
| 40–59                 | 814   | 157 (19.3)        | 59   | 50    | 33    | 14     | 1    |
| 60–200                | 493   | 194 (39.4)        | 77   | 44    | 27    | 45     | 1    |
| >200                  | 36    | 22 (61.1)         | 6    | 4     | 0     | 6      | 6    |
ongoing surveillance to track potential breakdowns in water
treatment or unknown sources of aluminum contamination
that might otherwise go undetected.20

Elevated serum aluminum concentrations might be
misinterpreted if caused by environmental contamination
during specimen collection or processing, as well as other
nonanalytic or analytic issues.14–17 While there is limited
information about the frequency of this problem, results
from this study suggest it may be a relatively common cause
for abnormal serum aluminum concentrations. Owing to
the retrospective study design, methods used by various
facilities could not be determined. However, since the
annual volume of serum aluminum measurements per
facility was low (median = 4.2, 90th percentile = 86.3), it is
likely that most, if not all, specimens were sent to reference
laboratories for aluminum measurements.

The proportion of elevated serum levels not related to
chronic exposure may further increase as the incidence of
toxic aluminum toxicity declines. For example, one study
involving 27 patients with serum aluminum levels between
100 and 200 μg/L reported that all results were below 60 μg/
L when retested within 6 weeks.19 This is similar to
observations in the present study in which 2 facilities had
clusters of elevated serum aluminum levels that mostly
reverted to normal upon follow-up testing in 2007 and 2011.

Previous studies31,32,34–36 have established that with chronic
aluminum intoxication even in the absence of further
exposure, a substantial decline in serum aluminum concen-
tration among dialysis patients is not expected for several
months or longer. Therefore, serum aluminum results that
were 60 μg/L or greater, a level at which treatment may be
indicated,2 were interpreted as unrelated to chronic toxicity
if a subsequent measurement within 45 days was below 20
μg/L. Table 3 describes the variability observed upon
repeated testing. Some of this variability is expected, owing
to the categorical nature of the data. It would be likely that
a proportion of retested specimens would move up or down 1
cutoff level, especially those starting out near the top or
bottom of the range. However, a few cases changed from
normal (<20 μg/mL) to toxic ranges (>60 μg/mL) upon
retesting. It would also be expected that this might also
represent false positives or in some cases, recent aluminum
exposures.

While there is no information or recommendations about
the optimal retesting interval to confirm chronic toxicity, we
observed no difference in the frequency of cases having
normal serum aluminum concentrations when additional
specimens were retested within 45 days or less or within 7
days or less. Furthermore, at least 40% of cases with
elevated serum aluminum levels were not associated with
chronic toxicity, and perhaps more if abnormal results below
60 μg/L would have also been considered. Finally, clusters of
elevated aluminum results observed among 2 different
facilities over short-term periods were in most cases not
consistent with chronic toxicity, since most demonstrated
nontoxic levels when tested later. These cases substantially
contributed to the overall frequency of elevated aluminum
levels observed among all patients in 2007 and 2011. For
these reasons, the incidence of genuine aluminum toxicity
reported in this study, and perhaps others, has likely been
overestimated.

There is no previous information about repeated testing
practices involving elevated serum aluminum levels that
address false-positive results. Guidelines issued by the
National Kidney Foundation7 in 2003 recommend follow-
up testing to access toxicity whenever a serum concentration
is between 60 and 200 μg/L. This includes performing 2
additional serum aluminum measurements, one at baseline
and another 2 days after deferoxamine (5 mg/kg) infusion.
The deferoxamine infusion test usually causes an increase in
serum aluminum concentrations, and an incremental rise of
50 μg/L or more is considered an abnormal result for
assessing toxicity and indication for treatment. While this
study was not designed to evaluate how often this
recommendation was followed, only 39% of patients for
whom serum aluminum concentrations were within 60 to
200 μg/L were retested within 45 days and of these, 38%
had subsequent results below 20 μg/L. Another study
involving 36 dialysis patients with toxic serum aluminum
concentrations found that 27 (75%) were retested within 6
weeks.19 These findings raise questions about how alumi-
num results are used in practice, which was beyond the
scope of this study. Nevertheless, this study suggests that
deferoxamine infusion testing may not be warranted as
based on a single elevated serum aluminum result. Instead,
an initial serum aluminum value in the toxic range should
be interpreted cautiously until confirmed by retesting
another specimen as soon as possible. For example, delaying
an infusion test until results from the baseline specimen are
available might be more effective for reducing costs and
risks to patients of undergoing potentially unnecessary
administration of deferoxamine. This practice should also
include assessment of collection, processing, and analysis
procedures to check for any breakdown that might have
contributed to falsely elevated results, such as use of an
incorrect collection container. Current guidelines for alumi-
num monitoring and treatment for toxic serum concentra-
tions might be improved by considering repeated testing to
exclude contamination or other causes for falsely abnormal
results before infusion testing.

This observational study has some limitations. Lacking
patient information, we were unable to confirm which of
these tests were performed in dialysis patients and which
were done for other reasons. However, since serum
aluminum testing is primarily indicated for monitoring
toxicity in dialysis patients, this reason likely accounted for
most of the cases. We were also unable to ascertain the
distribution of indications for testing such as routine
surveillance, targeted testing in patients taking aluminum-
containing medications, suspected problems with dialysis
water contamination, or evaluation of symptomatic patients.
Nevertheless, these factors would likely not affect the long-
range trends in the frequency of elevated serum levels
observed or in retesting practices. Finally, only a minority of
patients with elevated serum aluminum levels underwent
retesting, which may have affected the accuracy of estimated
rates of chronic aluminum toxicity.

In summary, this study shows that aluminum toxicity as
evaluated by serum concentrations has substantially de-
clined during the past 16 years in a large veteran population
and is comparable to what has been observed in other
studies. In addition, the frequency of serum aluminum
testing has declined over time in accordance with guidelines
for routine surveillance. However, based on observations
from repeated testing, a substantial proportion of elevated serum aluminum results are not associated with chronic toxicity, presumably owing to other causes such as transient exposure or problems related to collection, processing, analysis, or reporting errors. As a consequence, the incidence of aluminum toxicity assessed by serum concentrations in this study and perhaps others is likely overestimated. Repeated testing is recommended as the first step in response to an elevated serum aluminum concentration to prevent misinterpretation of results and the potential for diagnostic error.

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