

Hematological and Neurological Side Effects Associated with the Use of Aluminum Based Phosphate Binders in Dogs with Chronic Kidney Disease

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ABSTRACT

Hyperphosphatemia and secondary hyperparathyroidism are common in dogs with chronic kidney disease (CKD). It was hypothesized that dogs with CKD managed with aluminum-based phosphate binders accumulate aluminum, and may present clinical signs of toxicity. Fifty two client-owned dogs with CKD were examined in this retrospective study. Dogs diagnosed with CKD that were managed with aluminum based phosphate binders for at least 45 days and had complete blood count available were included, and followed for up to 120 days. Blood samples for aluminum concentration were drawn directly into plastic syringes using a newly placed peripheral intravenous catheter. The mean aluminum concentration for dogs was measured to 0.12 ± 0.13 ppm (range, 0.031–0.52 ppm) (reference range < 0.08 ppm). Eighteen dogs were suspected of having aluminum toxicity. The average aluminum daily dose in those dogs was significantly higher compared to dogs for which aluminum toxicity was not suspected (117.4 ± 63.7 vs. 71.5 ± 40.3 mg/kg/day, $P = 0.002$). Clinical signs suspected to result from aluminum toxicity were ataxia, altered mentation, paraparesis, tetraparesis, and decreased peripheral reflexes, decreased papillary light response and tremor. The most pronounced changes documented in dogs were progressive decrease in mean corpuscular volume and hemoglobin concentration. Both were found as reliable predictors of aluminum accumulation as well as sensitive and specific markers. It was concluded that dogs with CKD accumulate aluminum and are prone to aluminum toxicity. Progressive decrease in MCV and MCH should alert clinicians to aluminum accumulation. Dogs with advanced CKD managed with high aluminum doses should be screened routinely for aluminum accumulation.

Keywords: Hyperphosphatemia; Hyperparathyroidism; Binders; Neurological signs; Sevelamir; Lanthanum.

INTRODUCTION

Chronic kidney disease (CKD) is common in dogs (1). Hyperphosphatemia and secondary hyperparathyroidism are inevitable consequences and expected features of the disease (2). The latter has been shown to be associated with rapid progression of the disease in human patients and in dogs

(3, 4). Normalization of serum phosphorus concentration is a mainstay of the management of CKD, and is usually achieved by a combination of feeding low phosphate diets and administration of intestinal phosphate binding agents that further minimize intestinal absorption of phosphorus. Intestinal phosphate binding agents can be divided to alu-

minum based, calcium based or non-aluminum non-calcium based (e.g., sevelamer, lanthanum). The most commonly used phosphate binders in veterinary medicine are aluminum or calcium based. Both types are effective and inexpensive, but may promote adverse effects. Calcium based phosphate binders may cause or aggravate hypercalcemia, thus cannot be used in hypercalcemic patients or in patients that develop hypercalcemia during the treatment. Aluminum-based binding agents are used commonly in veterinary medicine because they are effective, inexpensive, and are associated with relatively few reported side effects. Nevertheless, as aluminum is eliminated primarily by the kidneys, patients with advanced CKD and reduced excretory capacity that are being supplemented with aluminum based phosphate binders may accumulate aluminum in their tissues in toxic concentrations. In contrast to the relatively limited reports of side effects associated with the use of aluminum based phosphate binders in veterinary medicine (5), aluminum toxicity is a well documented phenomenon in human CKD patients who are managed with aluminum based phosphate binders. It has been shown that human CKD patients who are managed with aluminum based phosphate binders accumulate aluminum in their body tissues, including in the brain (6). There is also an association between aluminum accumulation and the development of Alzheimer's disease (7). Reported side effects in human CKD patients include encephalopathy, microcytic anemia, and osteomalacia (8-12). These side effects have prompted a near discontinuation of aluminum-based phosphate binding agents in human CKD patients (13). Due to the risk for aluminum accumulation and toxicity, human CKD patients who are managed with aluminum-based phosphate binding agents are screened routinely for potential toxicity (14).

Aluminum is eliminated primarily by the kidneys; therefore, it is likely that dogs with CKD that are managed with aluminum based phosphate binders accumulate aluminum in their tissues, as has been documented in other species (5). A case report of two dogs with aluminum toxicity and their successful treatment with deferoxamine (Deferoxamine, 500mg/vial Inj., Desferal, Schaffhauserstrasse, Switzerland) has been published (5). The lack of recognition of aluminum toxicity in dogs is probably multi-factorial. Firstly, dogs may be less susceptible to aluminum toxicity compared to human patients. Secondly, human patients with more advanced CKD are being managed with high doses of aluminum based

phosphate binders and for longer periods compared to dogs. Thirdly, veterinarians may not be aware of this intoxication and thus may not recognize the symptoms associated with the disease. Fourth, signs of aluminum toxicity may be very subtle, as has been observed in human patients (e.g., speech disturbances and variable degrees of dementia) (15, 16), and consequently may go unnoticed in dogs or alternatively may be attributed to complication of the kidney disease *per se* (i.e. uremia, hypertension).

The objectives of this study were: 1) to assess whether dogs with CKD and treated with aluminum-based phosphate binding agents accumulate aluminum. 2) to characterize the side effects associated with the use of aluminum based phosphate binders, and 3) to identify early markers of aluminum accumulation that can alert clinicians to possible intoxication.

MATERIAL AND METHODS

Dogs

Dogs presented to the Medicine Service of the Veterinary Medical Teaching Hospital (VMTH) at UC Davis, California, and diagnosed with CKD were considered for inclusion. Chronic kidney disease was diagnosed based on persistent (> 4 weeks) renal azotemia, low urine specific gravity and chronic renal changes upon ultrasound examination. Only dogs managed for at least 45 days with aluminum based phosphate binders were included in the study. These dogs were followed as long as aluminum was administered for up to 120 days. Dogs for which a complete blood count (CBC) was not available at initiation of therapy or dogs that did not have at least two CBCs performed during the follow-up period were excluded from the study.

Laboratory data

Complete blood counts and serum chemistries were performed at the VMTH laboratory. In order to follow trends in complete blood count parameters for the first 120 days following aluminum initiation the data was portioned to 30-day intervals. When dogs had more than one value within each interval, parameters were averaged. When aluminum toxicity was suspected by the attending clinician, aluminum concentration was measured on serum samples at the Utah Veterinary Diagnostic Laboratory (Utah Veterinary Diagnostic Laboratory, Logan, UT, USA). Blood samples for aluminum concentration were drawn directly into plastic

syringes through newly placed peripheral intravenous catheter, to prevent contact of the sample with any form of glass or metal.

Statistical analysis

Normality of continuous variables was assessed using the Shapiro-Wilk test. Data were described as mean±SD when normally distributed and as median and range when not normally distributed. Continuous variables were compared between study groups using the student t-test when normally distributed and by the Mann-Whitney-U test when not normally distributed. The changes in the CBC parameters over time and the comparison between the study groups were performed using repeated measures ANOVA. The proportion of different abnormalities was compared between the study groups using the Chi square test. Correlations between the maximal drop in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) and the serum aluminum concentration was assessed using the Spearman rank correlation test. A receiver operating characteristics analysis was performed to assess the different variables as predictors of aluminum accumulation and to calculate the sensitivity and specificity. The optimal cutoff point was the point associated with the least number of misclassifications. Analysis was performed using a statistical software (SPSS 17.0 for Windows, Chicago, IL). For all tests applied, $P < 0.05$ was considered statistically significant.

RESULTS

Signalment

Fifty-two dogs fulfilled the inclusion criteria and were included in the study, of those 18 dogs were suspected of having aluminum toxicity. The mean age of all dogs was 7.9±4.1 years. Dogs that were suspected of having aluminum toxicity were significantly younger compared to dogs in which aluminum toxicity was not suspected (6.1±4.2 vs. 8.8±3.8 years, $P = 0.02$). Fourteen dogs were mixed breed and the rest were pure breed. There were 29 female dogs (all spayed) and 23 males (16 castrated). The mean body weight of all dogs was 21.2±13.8. There was a statistically significant difference in body weight between dogs in which aluminum toxicity was suspected and dogs that were not (26.4±17.7 vs. 18.4±10.6 kg, $P = 0.05$).

Overall, 21 dogs were managed with hemodialysis, at least partially, during the study period. The proportion of dogs that were managed with hemodialysis was significantly higher among dogs for which aluminum toxicity was suspected (61% vs. 42%, $P = 0.04$).

Aluminum dose and blood concentration

The average aluminum dose for all dogs was 87.4±53.7 mg/kg/day (range, 13.5-244.3 mg/kg/day). The average aluminum dose in dogs for which aluminum toxicity was suspected was significantly higher compared to those that were not suspected of having aluminum toxicity (117.4±63.7 vs. 71.5±40.3, $P = 0.002$). The average treatment time with aluminum in this study was 166±153.5 days with no statistically significant difference in the mean treatment time between dogs that were or were not suspected of having aluminum toxicity.

Aluminum serum concentration was measured only in dogs when aluminum accumulation/toxicity was suspected, based on the clinician discretion, mostly when dogs were medicated with aluminum based phosphorous binders for a relatively long period time, a high dose was used, or the dog presented neurological signs. The aluminum concentration was above the reference range in all dogs for which aluminum samples were obtained. The mean aluminum concentration of these dogs was 0.12±0.13 ppm (range, 0.031-0.52 ppm) (reference range <0.08 ppm). Iron and total iron binding capacity was measured in 15/18 dogs in which aluminum toxicity was suspected with an average of 172±224 µg/dL and 397±228 µg/dL, respectively.

Clinical signs associated with aluminum accumulation

Overall 18/52 dogs (34.6%), treated with aluminum hydroxide, were suspected of having aluminum toxicity/accumulation. Of these, nine dogs presented clinical signs that were suspected to result from aluminum toxicity. These included ataxia (4 dogs), altered mentation (2 dogs), paraparesis (2 dogs), tetraparesis (6 dogs), decreased peripheral reflexes (2 dogs), decreased papillary light response, and tremor (1 dog each). The remaining dogs were suspected of having aluminum toxicity/accumulation due to high dose of aluminum used and/or prolonged treatment time.

Clinicopathologic data

Initial serum creatinine for all dogs was 6.2±4.7 mg/dL. Serum creatinine was significantly higher in dogs for which

aluminum toxicity was suspected (8.9 ± 4.7 vs. 4.8 ± 2.9 mg/dL, $P < 0.001$, reference range 0.5-1.4 mg/dL). Phosphorus concentration prior to the initiation of treatment initiation was 9.1 ± 4.7 mg/dL (reference range 2.5-5.8 mg/dL), and was not significantly different between the two groups.

At initiation of therapy with aluminum based phosphate binders, the mean complete blood count parameters were all within the reference range with the exception of decreased hematocrit ($30 \pm 6.7\%$, reference range 37-55%). The average of the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and the mean corpuscular hemoglobin concentration (MCHC) were 68.0 ± 4.4 fl (reference range, 65-75), 23.4 ± 1.8 pg (reference range, 22-26), and 34.6 ± 1.5 g/dL (reference range, 33-36), respectively. The most pronounced complete blood count changes observed over the study period in all dogs were progressive decreases in MCV and MCH. During the initial 30, 60, 90 and 120 days the MCV decreased compared to the baseline in 1.1%, 4.5%, 7.1% and 9.1%, respectively (Figure 1). The decrease in MCV during the study period was significantly ($P < 0.001$) greater at all time points in dogs for which aluminum toxicity was suspected compared to dogs for which toxicity was not suspected and aluminum serum concentration was not obtained (2.6%, 8.5%, 12.9%, 15.7% compared to 0.06%, 2.4%, 3.3%, 5.1%) (Figure 2). Repeated measures ANOVA revealed significant ($P < 0.001$) interaction between the two groups, with dogs in which aluminum toxicity was suspected having a more rapid decrease in MCV over time compared to dogs in which toxicity not suspected. The maximal change observed in MCV during the study period for all dogs was $10.5 \pm 7.8\%$, for dogs with suspected aluminum toxicity $15.6 \pm 8.7\%$ and for dogs with no suspected toxicity $7.7 \pm 5.8\%$. There was a statistically significant difference in the maximal drop in MCV between the two latter groups ($P < 0.001$). No significant correlation was found between the maximal drop in MCV and the aluminum serum concentration in dogs when it was available. The prevalence of microcytosis (MCV < 65 fl) also increased during the study period. After 30, 60 and 90 days of aluminum administration the proportion of microcytosis was 32%, 61% and 75%, respectively. Finally, the maximal change in MCV was found to be a good predictor of aluminum accumulation. An ROC analysis revealed an area under the curve (AUC) of 84%. An MCV of 58 fl was found to be the optimal cutoff point, corresponding to sensitivity and specificity of 78% and 85%, respectively.

The trend in the MCH was a similar to that trend observed for MCV, with significant decrease in MCH over time, significant difference between the two groups and a significant interaction between the groups. The maximal change in MCH for all dogs was $9.4 \pm 8.5\%$, for dogs with suspected aluminum toxicity $14.3 \pm 9.1\%$ and for dogs that were not suspected of toxicity $6.9 \pm 7.0\%$. As in MCV, there was a statistically significant difference between the two latter groups ($P < 0.001$). The maximal change in MCH was also found a good predictor of aluminum accumulation with an AUC of 87%. The optimal cutoff point was MCH of 18pg, corresponding to sensitivity and specificity of 83% and 97%, respectively.

Contrary to MCV and MCH, there were no statistically significant changes over time in MCHC and in hematocrit during the initial 120 days from initiation of aluminum based phosphate binders. Iron and total iron binding capacity were not measured routinely in the entire study population, nonetheless, it was available in 12 of the 18 dogs that were suspected to have aluminum toxicity and was found to be within the reference range in all.

DISCUSSION

This current study has demonstrates that aluminum, when administered to dogs with CKD to control hyperphosphatemia and secondary hyperparathyroidism, accumulates in dogs, and may be associated with clinical signs. Therefore, proper monitoring and awareness are required.

Chronic kidney disease is common in dogs, and hyperphosphatemia is an expected and inevitable consequence of the disease (4). Phosphorous restricted diets and phosphate binding agents are the mainstay of therapy of hyperphosphatemia and secondary hyperparathyroidism (17). Aluminum hydroxide has been used routinely in veterinary patients as a phosphate binding agent; however toxicity was rarely documented (5), thus is considered safe in dogs and cats. It is plausible that the apparently low frequency of aluminum toxicity documented in dogs compared to human patients relates to lower doses of aluminum used in dogs, shorter periods of administration time, less advanced kidney dysfunction, species differences, and a combination of the above. It is also possible that the apparently lower incidence of aluminum toxicity relates to clinicians' awareness of this problem and the misconception that aluminum accumulation does not exist in dogs.

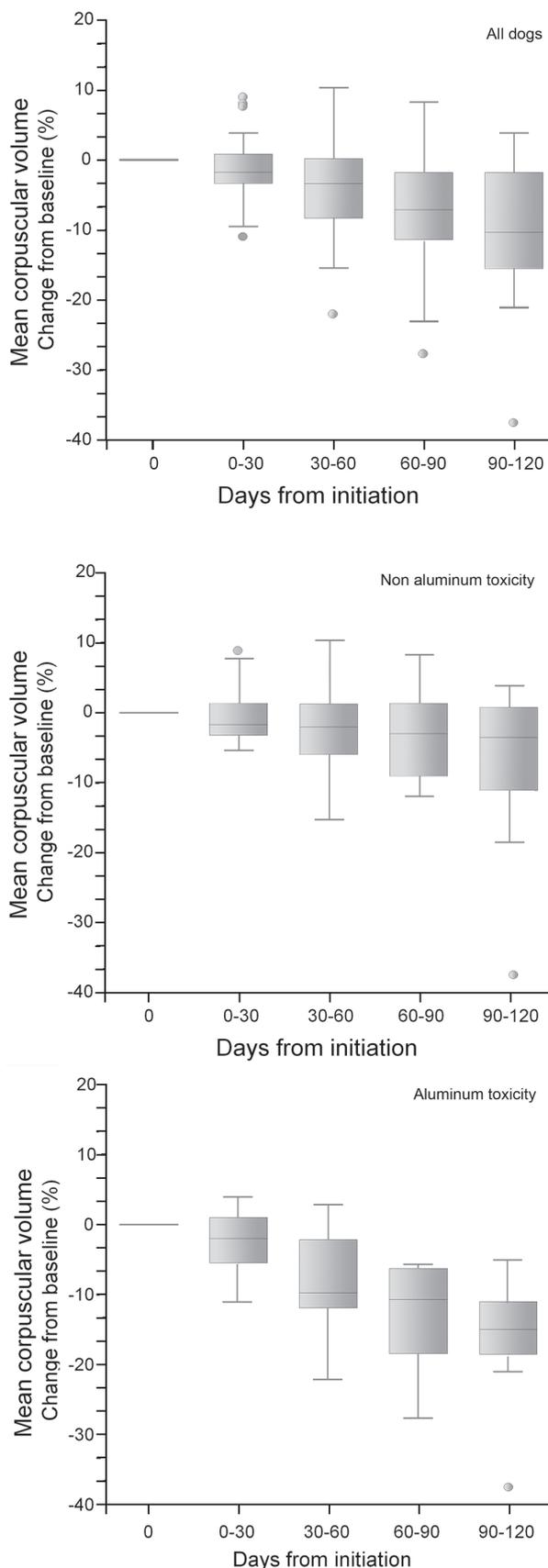


Figure 1:

- a:** Changes in mean corpuscular volume over time of all dogs receiving aluminum based phosphorous binders.
- b:** Changes in mean corpuscular volume over time of dogs receiving aluminum based phosphorous binders and not suspected of having aluminum toxicity.
- c:** Changes in mean corpuscular volume over time of dogs receiving aluminum based phosphorous binders suspected of having aluminum toxicity.

In animals, aluminum salts are probably less likely to achieve concentrations associated with overt clinical manifestations due to relatively short life spans or due to sub-therapeutic doses. Nevertheless, guidelines for control of serum phosphorus concentration in dogs with CKD have become more exacting, necessitating the use of high doses of phosphate binders. In addition, as knowledge increases, animals with advanced disease can now be managed for longer period of times. The combination of high doses of aluminum based phosphate binders and longer periods of administration in dogs with limited excretory capacity increases the risk of aluminum toxicity. In the current study, dogs in which aluminum toxicity was suspected, had a more severe azotemia (i.e., lower excretory capacity), and were managed with significantly higher mean aluminum hydroxide doses, compared to those that were not suspected of having aluminum accumulation. These findings demonstrate that the combination of a high aluminum hydroxide dose in dogs with severe kidney dysfunction predispose these dogs to aluminum accumulation. Moreover, serum aluminum concentrations were invariably above the reference range when measured, indicating that dogs with advanced CKD that are managed with aluminum based phosphate binders, do in fact accumulate aluminum, as has been shown in human patients. It is likely that the true incidence of dogs that have significant aluminum accumulation is higher than documented in this study as only a subset of patients had their aluminum serum concentration measured. On the other hand the high prevalence documented in this study might have been influenced by the VMTH being a tertiary referral center. Consequently, patients presented with more advanced kidney disease, and, possibly, higher doses of aluminum based phosphate binders are more readily prescribed.

In the current study, 21 dogs were managed, at least partially, during the study period with hemodialysis. It has been

shown that aluminum accumulation in human patients who are managed chronically with hemodialysis may be due to aluminum contamination of the dialysate (14). In the current study hemodialysis probably did not play a role in aluminum accumulation, even in patients that were managed with hemodialysis for a long period of time, as the water quality was routinely measured and aluminum was always undetectable. Nevertheless, in patients treated chronically with hemodialysis this possibility should always be considered. The high prevalence of aluminum accumulation among dogs managed with hemodialysis is probably related to the higher degree of renal dysfunction of these patients, higher doses of aluminum hydroxide used, increased awareness of clinicians managing these dogs, or a combination of the above.

The clinical signs that were attributed to aluminum accumulation were mostly neurologic and included ataxia, altered mentation, paraparesis/tetraparesis and decreased peripheral reflexes. It cannot be excluded that other more subtle clinical signs, as observed in human patients with aluminum accumulation, were more prevalent among dogs with aluminum accumulation, but went unnoticed or alternatively were not attributed to aluminum accumulation. Therefore, it is the authors' opinion that aluminum accumulation should be considered in the differential diagnoses for all dogs with

CKD that are managed with aluminum-based phosphate agents, even when only subtle neurological signs are present. Moreover, in the presence of advanced CKD and the use of high doses of aluminum binders, routine screening for serum aluminum concentration should be considered, as is recommended for human patients (18).

The most common clinicopathologic abnormalities observed in the study were progressive microcytosis and progressive decrease in MCH. The decrease in both parameters was significantly higher among dogs in which aluminum toxicity was suspected, implying a possible correlation between the degree of aluminum accumulation and the degree of microcytosis. Nevertheless, there was no statistically significant correlation between the maximal drop in MCV and the measured serum aluminum concentration. This finding may be related to the partial correlation between the serum aluminum concentration and the tissue concentration (19). Progressive microcytosis is also a well documented phenomenon in human patients with aluminum toxicity and in animal models (20). The exact pathophysiology of microcytosis associated with aluminum toxicity is undetermined, however it is suggested that increased aluminum concentrations may interfere with iron metabolism, since the decrease in MCV is similar to the expected with iron deficiency, however, iron supplementation cannot reverse or prevent the microcytosis associated with aluminum toxicity (21). The cause of progressive microcytosis may be difficult to distinguish initially from iron deficiency associated with erythropoietin therapy in uremic animals (22). Nevertheless, in the current study the routine use of iron dextran along with the erythropoietin therapy make iron deficiency less likely to be the cause for the progressive microcytosis. Since progressive microcytosis is a consistent finding among species (e.g., human, rodents, dogs) (21, 23, 24) it is likely that the presence of microcytosis can be used as an early indicator for aluminum accumulation in CKD patients treated with aluminum-based phosphate binders after the exclusion iron deficiency. This is further supported by the high area under the ROC curve and high sensitivity and specificity of MCV as predictor of aluminum accumulation.

The elimination of aluminum from uremic animals that are symptomatic for aluminum toxicity remains problematic. Aluminum discontinuation should be the first step when toxicity is suspected or documented. Deferoxamine has been used successfully as an aluminum-chelating agent in human

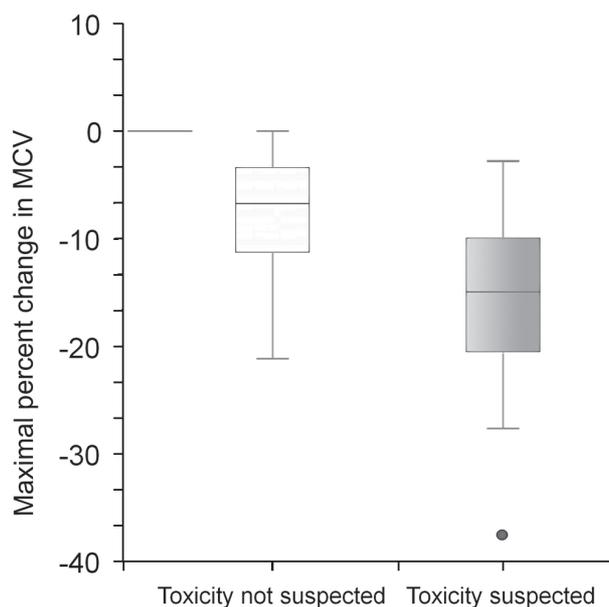


Figure 2: Maximal documented decrease in MCV from baseline (in percentage) of all dogs receiving aluminum based phosphorus binders. The reference MCV was the one documented just before the initiation of aluminum based phosphorous binders.

patients, laboratory animals and in dogs (5, 25, 26). The coupling of deferoxamine chelation with hemodialysis is likely more effective, since the kidney is the primary route for the elimination of the chelated aluminum, and its clearance will be significantly impaired in patients with poor renal function (26).

There are a few limitations to this study. First, the number of dogs for which aluminum concentration was available is limited decreasing the power of the statistical comparisons. Second, clinical signs that might have resulted from aluminum toxicity may not have been attributed to aluminum accumulation, due to a lack of awareness, thus the incidence of aluminum toxicity might have been an underestimation of its true prevalence. Third, this is not a controlled study, therefore some of the clinical signs and clinicopathologic abnormalities that were attributed to aluminum accumulation might not have been related to aluminum administration alone, but rather were a consequence of the kidney disease *per se*. Thus, the association between aluminum and clinical and clinicopathologic signs can be pointed out, but a cause and effect relationship cannot be proven. Nevertheless, based on the current knowledge, most of the observed signs were less likely to develop due to kidney disease in the absence of aluminum administration. Fourth, in some cases, aluminum blood concentration might have been obtained after a progressive microcytosis, which was refractory to iron supplementation, was noted; therefore, in these dogs microcytosis might have been the trigger to suspect aluminum accumulation. If this was the case, the prevalence of microcytosis might have been higher in dogs in which aluminum toxicity was suspected due to bias by selection. Fifth, aluminum concentration was not measured in all dogs in the current study, thus it cannot be excluded that some of the dogs for which aluminum accumulation was not suspected had high aluminum concentration as well, and therefore were not included in the dogs with aluminum toxicity. Finally, tissue aluminum concentration was not measured in any of the dogs in this study thus the correlation between tissue and blood aluminum concentration cannot be made.

In summary, aluminum accumulates in dogs with CKD that are managed with aluminum based phosphate binders, as has been shown in other species. All dogs in this study that had their aluminum blood concentration measured had abnormally high concentrations. Neurological signs were the most common clinical manifestation of dogs with alu-

minum accumulation, however, these were not consistent within the study group, thus the possibility for aluminum accumulation should be suspected in any dog with CKD that is managed with aluminum based phosphate binders and presents neurological signs. The most common clinicopathologic abnormalities noted were progressive microcytosis and a decrease in MCH, therefore the aforementioned findings (when refractory to iron supplementation) can be used as early indicators of aluminum accumulation.

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