Entry, Half-Life, and Desferrioxamine-Accelerated Clearance of Brain Aluminum after a Single $^{26}$Al Exposure

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The objectives of our study were to estimate the percentage of aluminum (Al) that enters the brain, the half-life of brain Al, and the ability of an Al chelator to reduce brain Al. Rats received an iv infusion of Al transferrin, the primary Al species in plasma, or Al citrate, the predominant small molecular weight Al species in plasma. The infusion contained $\sim 0.2 - 0.3$ nCi (0.4 - 0.6 nmol) $^{26}$Al, enabling the study of Al distribution into and retention by the brain at physiological Al concentrations. Some Al transferrin–infused rats received ip injections of the Al chelator desferrioxamine (DFO), 0.15 mmol/kg, three times weekly. The others received saline injections. The rats were euthanized from 4 hr to 4 days (Al citrate) or 256 days (Al transferrin) later. Brain $^{26}$Al was determined by accelerator mass spectrometry. Peak brain $^{26}$Al concentration was $\sim 0.005\%$ of the $^{26}$Al dose in each gram of brain, irrespective of Al species administered. In the absence of DFO treatments, brain $^{26}$Al concentration decreased with a half-life of approximately 150 days. The brain Al half-life in the DFO-treated rats was approximately 55 days. The results show a small fraction of Al in blood enters the brain, where it persists for a long time. The ability of repeated DFO treatments to modestly accelerate the reduction of brain Al is consistent with the necessity of prolonged DFO therapy to significantly reduce Al-induced dialysis encephalopathy.

Key Words: accelerator mass spectrometry; aluminum; brain; chelation therapy; desferrioxamine; half-life; rat.

Aluminum (Al) is a neurotoxicant that can contribute to uremia- and dialysis-associated disorders of the brain (dialysis encephalopathy) and bone (aluminum-associated bone disease; Alfrey et al., 1976; Bushinsky, 1997; Crapper McLachlan et al., 1991). It has been suggested to play a role in the etiology of some neurodegenerative diseases, including Alzheimer’s disease (AD). This is highly controversial (reviewed in Yokel, 2000). It is assumed that the neurotoxicity of Al is due to its presence in the brain. The application of accelerator mass spectrometry (AMS) to the analysis of $^{26}$Al (Flarend and Elmore, 1998) has enabled the study of Al toxicokinetics under physiological conditions (Yokel and McNamara, 2001). $^{26}$Al has been found in the brain after its ip (Kobayashi et al., 1990) or iv injection (Walker et al., 1994) and after oral administration under conditions that simulate Al consumption in drinking water (Driëke et al., 1997; Fink et al., 1994; Jouhanneau et al., 1997; Walton et al., 1995). However, these were all limited studies, employing a small number of rats and/or a single time. They are summarized in the Discussion section. They do not provide a confident estimate of the percentage of Al that enters the brain from systemic circulation. Therefore, the first objective of this study was to determine the percentage of Al that enters the brain from systemic circulation. This was accomplished by determination of peak brain $^{26}$Al concentration after its iv administration. The $^{26}$Al was introduced intravenously either as an Al-transferrin complex, to model the predominant chemical species of Al in the plasma where $> 90\%$ of Al is bound to transferrin, or as Al citrate, the predominant small molecular weight Al species in plasma (Yokel and McNamara, 2001).

The residence time (organ half-life) of Al in the brain has not been previously reported. It was concluded that “the available data are fully consistent with a very slow normal accumulation of Al" at the organ level in the brain” as a result of a very slow uptake of Al" in the brain paired with minimal or nonexistent brain Al elimination (Ganrot, 1986, p. 394). Only two of the above studies determined brain $^{26}$Al at more than one time point. A slight increase of brain $^{26}$Al was observed from 5 to 35 days after its ip administration (Kobayashi et al., 1990), whereas brain Al decreased $\sim 6$-fold from the 5th to the 30th day after oral $^{26}$Al administration (Jouhanneau et al., 1997). A reliable estimate of brain Al half-life cannot be determined from these results. Therefore, a second objective was to estimate the half-life of Al in the brain. This was calculated from brain $^{26}$Al concentration determined from 4 hr to 256 days after iv administration of $^{26}$Al transferrin.

The third objective was to study the effect of desferrioxam-
ine (DFO) on brain Al half-life. Therefore, some rats were given repeated injections of DFO to assess the ability of brain aluminum to be mobilized. Brain Al half-life was calculated under this condition. The results address the demonstrated benefit of prolonged DFO therapy to reverse dialysis encephalopathy and the potential of chelation therapy to reduce brain Al in Alzheimer’s disease.

MATERIALS AND METHODS

Animal procedures. The subjects were 100 male Fisher 344 rats, weighing 268 ± 27 g (mean ± SD), at the time of 26 Al or control dosing. The University of Kentucky Institutional Animal Care and Use Committee approved the animal work. The research was conducted in accordance with the Guiding Principles in the Use of Animals in Toxicology.

All rats were implanted with a femoral cannula 1 day prior to the iv infusion of 26 Al transferrin, 26 Al citrate, or vehicle. This enabled Al administration in the absence of anesthetics, as previously described (Yokel et al., 2001). Seventy-four rats received iv 26 Al transferrin infused over 1 h. They were euthanized from 0.17 to 256 days after 26 Al dosing, specifically at 5, 10, 20, 30, 40, 120, 256 (n = 12), 128 (n = 12), and 256 (n = 12) days. Beginning on the third day after the 26 Al transferrin infusion, half of the rats in each group received ip DFO (0.15 mmol/kg) three times weekly. Desferrioxamine mesylate (Desferal®) was provided by Hanspeter Nick, Novartis Pharma AG, Basel, Switzerland. This was dissolved in saline immediately before administration. The other 26 Al-infused rats received saline injections on the same schedule. Twelve control rats received identical treatment, although the Al transferrin did not contain 26 Al. Six received saline injections and six received DFO injections. Two of each group were euthanized 64, 128, and 256 days after 26 Al transferrin dosing.

To determine whether the chemical species of the administered 26 Al significantly influenced its distribution into the brain, 14 rats received an iv infusion of 26 Al citrate, administered under the same conditions as the 26 Al transferrin. They were euthanized at 4 h (0.17 days; n = 4), 1 day (n = 5), and 4 days (n = 5).

Aluminum transferrin and aluminum citrate preparation. To prepare 26 Al transferrin, Al as 26 Al or 27 Al in solution in the presence of chloride, was incubated at 37°C for 1 h with 37 μM transferrin. Also present were 630 μM albumin, 99 μM citrate, 1100 μM phosphate, 1370 μM Ca, 580 μM Mg, 50 mM HCO3, and sufficient NaCl to produce an isotonic mock plasma. The iv infusion contained 0.19–0.33 nCi (10–17.5 ng; 0.37–0.65 nmol) of 26 Al in 1 ml mock plasma. In the presence of transferrin, the procedure produced transferrin-bound Al, verified by ultrafiltration of the resultant solution. Only 20–30% of the Al was ultrafilterable, consistent with transferrin binding of 70–80% of the Al. Additionally, the absorbance peak of transferrin at 295 nm was shifted to 300 nm after incubation with Al under these conditions, providing further evidence of formation of the Al-transferrin complex. The mock plasma, with 26 Al- or 27 Al transferrin, was prepared immediately before its administration.

To prepare 26 Al citrate, 0.33 nCi 26 Al was incubated with a 0.5-ml solution containing 198 μM citrate and 1.8% NaCl at 37°C for 1 h. An equal volume of sterile water was then added to produce an isotonic solution containing the same citrate concentration as plasma. In the absence of other ligands, Al would be expected to associate with citrate.

Sample preparation for 26 Al determination. The rats were anesthetized by ketamine/xylazine injection and exsanguinated. Blood was obtained from 26 Al–infused rats euthanized at 0.17 and 1 days, and from 26 Al transferrin-infused, saline-treated rats euthanized up to day 16. Serum was obtained. Serum samples were prepared for 26 Al determination as described (Yokel et al., 2001). The brain was removed. The meninges, olfactory bulb, cerebellum, and brain stem were removed. Each brain and an aliquot of serum were transferred to a scrupulously cleaned, preweighed, 7-ml Teflon screw-cap container (Tuf-Tainer®) and weighed. Four milligrams 27 Al (ICP/DCP standard, Aldrich) was added to each sample to enable determination of the 26 Al:27 Al ratio. The sample was dried, digested in 3 ml of a 2:1 v/v HNO3:HClO4 mixture, and the liquid then evaporated. We found that ashing brain resulted in a glasslike material believed to be Al oxyphosphate. We therefore developed a procedure that separates Al from phosphate (Brauer et al., 1999). This was used to prepare brain samples for 26 Al determination. The Al-containing sample was ashed at 1000°C to prepare Al2O3 for 26 Al analysis.

Analysis of 26 Al by AMS. The 26 Al:27 Al atom ratio was determined using the AMS technique by the Purdue Rare Isotope Measurement Laboratory (PRIME Lab; Sharma et al., 2000). Replicate brain samples were prepared by infusing four rats with a total of ~ 2 nCi (100 ng; 4 nmol) 26 Al as 27 Al transferrin. They were euthanized 1 day later. Their brains were combined with the brains from 7 nontreated rats to produce the desired volume of brain tissue, which was homogenized and divided into 11 aliquots. Four aliquots analyzed by AMS had an RSD of 3.8%, demonstrating reproducible within-batch procedures. Aliquots processed with the brain samples from rats euthanized 0.17–256 days after 26 Al transferrin administration were within 10% of the mean of the original four aliquots, demonstrating acceptable across-batch procedures. All brain samples from 26 Al-treated rats were measured until the AMS error was < 10% (mean ± SD = 4.2 ± 1.6%). Serum samples from 26 Al-transferrin-infused, saline-injected rats and Al-citrate-infused rats were measured until the error was ≤ 12% (mean ± SD = 4.8 ± 2.1%).

Data analysis. Brain 26 Al was corrected for the presence of 26 Al in the blood within the brain, based on the regional blood volume of the frontal lobe (Ohno et al., 1978).

Simple regression analyses of brain Al concentration versus time (from 4 to 256 days after 26 Al dosing) for the saline-treated rats as well as the DFO-treated rats were conducted to determine if brain Al significantly changed over time. One- and two-way ANOVAs were conducted of the same brain 26 Al concentrations, using the SAS GLM procedure. The two variables were saline treatment versus DFO treatment after 26 Al transferrin infusion and time. Individual results were used in these calculations.

The half-lives of brain Al in saline- and DFO-treated rats were determined using RSTRIP. This is a program for compartmental modeling and kinetic analysis that combines the functions of exponential stripping for obtaining initial parameter estimates, least squares refinement of parameter values, and interactive graphics (Fox and Lamson, 1989).

RESULTS

Serum 26 Al decreased after iv 26 Al transferrin administration from 82 × 10−15% of the dose/ml blood 4 h after infusion to 2 × 10−15% 16 days later (Fig. 1, upper panel). Serum 26 Al 4 h and 1 day after 26 Al citrate infusion was ~ 53% and 67% of that seen after Al transferrin. Brain 26 Al initially increased after 26 Al transferrin administration before peaking at ~ 5 × 10−34% of the dose/g brain (Fig. 1, upper panel). Brain 26 Al after 26 Al citrate administration paralleled that seen after 26 Al transferrin, also peaking at ~ 5 × 10−34% of the dose/g brain. Brain 26 Al concentration then decreased to ~ 30% and 10% of its peak concentration in the saline- and DFO-treated rats 256 days later (Fig. 1, lower panel). None of the 12 brain samples from the non–26 Al-treated control rats demonstrated negligible contamination, ~ 2 to 58 × 10−7% of the injected dose. This is < 1% of the 26 Al seen in the brain samples of the 26 Al-treated rats with which they were paired. Three of the control brain samples, which were processed concurrently, had more contamination, ~ 4 × 10−4% of the injected dose, representing 6–17%
of that seen in paired rats. Therefore, contamination did not significantly influence the results of this study.

The regression analyses of brain $^{26}$Al concentration versus time were significant for both the saline-treated, and the DFO-treated, $^{26}$Al transferrin-injected groups ($p < 0.0001$). Calculation of the terminal brain $^{26}$Al half-life yielded values of 150 and 55 days in the absence and presence of DFO treatment, respectively. The ANOVAs showed significant effects of both time ($p < 0.0001$) and treatment ($p < 0.01$). The interaction was not significant. Brain $^{26}$Al concentration was statistically different between saline-treated rats euthanized on day 256 compared to all previous days. Statistically significant differences were seen for DFO-treated rats, as follows: day 32 versus day 4; day 64 versus days 4 and 16; day 128 versus days 4 and 16; and day 256 versus all previous days. Brain $^{26}$Al concentration was statistically different between saline-treated and DFO-treated rats euthanized on days 64 and 128.

**DISCUSSION**

The objectives of this study were 3-fold: to quantitate brain Al entry from systemic circulation, to estimate the residence time of Al in the brain, and to determine if repeated treatment with an Al chelator influences the brain Al half-life.

Rat brain $^{26}$Al entry was comparable after $^{26}$Al transferrin and $^{26}$Al citrate administration. These results are likely due to the preferential association of Al for transferrin over citrate in plasma (Martin, 1986), resulting in $\geq 90\%$ of Al bound to transferrin at equilibrium, as noted above. This reaction occurs in minutes (Wes Harris, personal communication).

Prior to the present study, there were two published reports of brain $^{26}$Al after systemic and four after oral $^{26}$Al administration. These are summarized in Table 1 and Table 2. Kobayashi et al., (1990) administered the $^{26}$Al by ip injection. This may have resulted in Al precipitation in the peritoneal cavity, producing $\geq 100\%$ bioavailability. Blood $^{26}$Al decreased 40-fold, from 4 h to 16 days, after iv $^{26}$Al injection, consistent with slow release of $^{26}$Al from the peritoneal cavity. In contrast, blood $^{26}$Al decreased 40-fold, from 4 h to 16 days, after iv $^{26}$Al.

**TABLE 1**

<table>
<thead>
<tr>
<th>Time after</th>
<th>No. of</th>
<th>% of dose per</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>injection (days)</td>
<td>rats</td>
<td>g brain ($\times 10^3$)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.6</td>
<td>Kobayashi et al., 1990</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1.0</td>
<td>Kobayashi et al., 1990</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>0.9</td>
<td>Kobayashi et al., 1990</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>0.6</td>
<td>Kobayashi et al., 1990</td>
</tr>
<tr>
<td>35</td>
<td>1</td>
<td>1.2</td>
<td>Kobayashi et al., 1990</td>
</tr>
<tr>
<td>21</td>
<td>1 normal</td>
<td>5</td>
<td>Walker et al., 1994</td>
</tr>
<tr>
<td>21</td>
<td>1 uremic</td>
<td>2</td>
<td>Walker et al., 1994</td>
</tr>
</tbody>
</table>

*Note. Values are reported as % of the dose per g brain, $\times 10^3$. |

**TABLE 2**

<table>
<thead>
<tr>
<th>Time after dosing (days)</th>
<th>No. of rats</th>
<th>% of dose per g brain ($\times 10^3$)</th>
<th>% of dose per g brain $\div 0.003$ (L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>2</td>
<td>6</td>
<td>2.0</td>
<td>Fink et al., 1994</td>
</tr>
<tr>
<td>14</td>
<td>8 $^a$</td>
<td>7</td>
<td>2.3</td>
<td>Walton et al., 1995</td>
</tr>
<tr>
<td>2</td>
<td>8 $^b$</td>
<td>2</td>
<td>0.7</td>
<td>Dru¨eke et al., 1997</td>
</tr>
<tr>
<td>2</td>
<td>4 $^c$</td>
<td>54</td>
<td>18</td>
<td>Dru¨eke et al., 1997</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>6</td>
<td>2.0</td>
<td>Jouhanneau et al., 1997</td>
</tr>
<tr>
<td>15</td>
<td>2</td>
<td>3</td>
<td>1.0</td>
<td>Jouhanneau et al., 1997</td>
</tr>
<tr>
<td>30</td>
<td>2</td>
<td>1</td>
<td>0.3</td>
<td>Jouhanneau et al., 1997</td>
</tr>
</tbody>
</table>

*Note. Values are reported as % of the dose per g brain $\times 10^3$. Values have been divided by 0.003 to model oral aluminum bioavailability of 0.3%.

$^a$Thirty-hour food deprivation.

$^b$Free food access.

$^c$Twenty-four-hour food deprivation.
infusion in the present study (Fig. 1, upper panel). In the study of Walton et al. (1995), brain $^{26}$Al concentrations of two of the $^{26}$Al-dosed rats were comparable to controls, whereas brain $^{26}$Al in the other six $^{26}$Al-dosed rats ranged up to 250-fold higher. To compare brain $^{26}$Al after oral and parenteral $^{26}$Al administration, the results obtained after oral dosing have been divided by 0.003, the estimate of oral Al bioavailability from water (Yokel et al., 2001). The results are reasonably similar (Table 1 and Table 2). It appears that, under physiological conditions, $\sim 1.5 \times 10^{-3}$ % of the Al in blood enters each gram of rat brain. This does not appear to be significantly influenced by the route of administration or the chemical form when administered as soluble Al.

The present results are the first estimate of the half-life of Al elimination from the brain. The half-life estimate for the saline-treated rats is not definitive, because the duration of sampling from which it was calculated was not three times as long as the calculated half-life, as would be desired. The results show a very slow clearance of brain Al over time in the absence of chelation treatment. Previous observations have suggested that the clearance of Al from the brain might be prolonged. Brain Al concentration in 3 rats 1 year after intracranial Al injection was 2 $\mu$g/g dry brain, compared to 16.2 $\mu$g/g in 13 rats shortly after the injection and 1.1 $\mu$g/gm in nontreated rats (Crapper et al., 1980). This group also found a brain Al concentration of 4.7 $\mu$g Al/g in one cat 3 years after intracranial Al injection, which was 67% of that seen 2 weeks after the injection, suggesting slower brain Al clearance in the cat than in the rat. In the human, brain Al was elevated postmortem in former dialysis patients who had successful renal transplants years prior to their death (McDermott et al., 1979). Similarly, 12 of 13 chronic renal failure patients had evidence of stainable brain Al up to 10 years after successful renal transplantation, whereas none of the controls demonstrated brain Al by this method (Reusche et al., 1996). The subcellular localization of the Al-containing deposits in the chronic renal failure patients was intracytoplasmic, which may have been in granules of lysosomal origin (Reusche et al., 1996). Comparison of Al in nuclei and chromatin suggested the Al was largely intranuclear in control humans, concentrated in cell nuclei of Alzheimer subjects, and lower in the nuclei of dialysis encephalopathy victims than the other two groups (Crapper et al., 1980). Human neuroblastoma cells maintained for 8 days in a medium containing $^{26}$Al-EDTA had approximately equal Al concentrations in the nuclear sap and cytoplasm (Dobson et al., 1998). There are no comparable studies in glial cells, which have been proposed to be a significant target of Al neurotoxicity (reviewed in Yokel, 2000). The intracellular endogenous Al ligands are unknown. Therefore, it is not known whether the Al that persists in the brain contributes to neurotoxicity.

Although there is no previous report of the brain Al half-life, there are reports of Al persistence in the mammal. Half-lives of 8 days in the kidney and 16–24 days were observed in rat liver, muscle, spleen, and tibia (Greger et al., 1994). The half-life increased with age, from 9 to 12 to 16 days in kidney and 38 to 58 to 173 days in tibia of the 2-, 8-, and 19-month old rat (Greger and Radzanowski, 1995). Bone Al determined in two rats at each of 10 times from 0.5 to 30 days after oral ingestion of $^{26}$Al peaked $\sim 2$ h after ingestion, decreased slightly by 6 h, and then did not appear to change over the next 30 days (Jouhanneau et al., 1997). Half-lives of 44, 74, and 113 days were estimated for lung, liver, and spleen from tissue Al concentrations obtained up to 128 days after a single $^{26}$Al infusion in the rabbit (Yokel and McNamara, 1989). There was a half-life in the kidney that greatly exceeded 100 days. Data from humans suggest the presence of one or more compartments with a terminal half-life of 0.7–7.9 years (Ljunggren et al., 1991). After a single human volunteer received an iv injection of $^{26}$Al and citrate, the apparent whole-body half-life estimated 3 years later was $\sim 6.5$ years (Priest et al., 1995). This prolonged whole-body half-life suggests a deep compartment from which the Al slowly distributes. Approximately 70% of the human’s Al body burden is in the skeletal system, based on a bone Al concentration of 5–10 mg/kg in the adult (Garfot, 1986) and composition of 11.6% of body weight by bones (Ludwig, 1979). Storage of a major fraction of the body burden of Al in bone and the apparent long half-life of bone Al (Greger and Radzanowski, 1995; Jouhanneau et al., 1997) suggest bone Al may greatly influence the half-life of Al elimination from the whole body and the brain. Alternatively, prolonged storage of Al in neurons, a postmitotic cell, perhaps concentrated in the lysosomes, may account for Al persistence in the brain.

Repeated Al exposure paired with Al persistence would produce Al accumulation over the life span. Indeed, there is evidence for an age-related increase of the human lung Al concentration, which is attributed to inhalation and retention of dust particles (Alfrey et al., 1980; Stitch, 1957; Tipton and Shafer, 1964) as well as Al in the liver and the kidney to a small extent (Stitch, 1957). Brain Al increased from 1.6 $\mu$g Al/g dry weight in three 25- to 65-year-old subjects to 2.7 $\mu$g Al/g in six 75- to 99-year-old subjects (McDermott et al., 1979) and increased $\sim 2$-fold from the seven humans < 6 months old to four who were > 80 years old (Markesbery et al., 1984). In contrast, no correlation was observed between age and lung Al concentration of 16 Americans, or between age and bone, brain gray matter, heart, muscle, liver, or spleen Al concentration in 21 Australians or 16 Americans (Alfrey et al., 1980). No correlation between age and brain Al concentration was observed in four 58- to 74-year-old humans (Jacobs et al., 1989). Mean serum Al concentration increased $\sim 55\%$ from age 20–80 years in 356 healthy humans (Zapatero et al., 1995). In contrast, no relationship was seen between age and serum Al concentration in 76 humans age 21–83 years or whole blood, urine, or hair of 42 humans age 21–83 years (Naylor et al., 1990). Except for lung, the increase of Al with age was $\approx 2$-fold in the above studies. The lack of significant findings in the studies of few subjects and/or a more limited
age range is not surprising, considering the small age-related increase of Al when a significant correlation was found, inter-subject variability, and the difficulty of measuring low concentrations of $^{27}$Al due to its ubiquitous presence.

It is not possible to use the present animal data to predict the human brain Al half-life with any confidence. The typical approach to apply pharmacokinetic results obtained in nonhuman mammals to the human is to use interspecies scaling (McNamara, 1991). One approach is allometric scaling based on maximum life span. This would suggest a human brain Al half-life of ~12 years. The limited reports of tissue half-lives in rat, rabbit, and human, (above) suggest the Al half-life increases across these species. However, there is insufficient data on brain half-lives of metals in mammalian species to predict human brain Al half-life from the present data with any confidence.

Repeated DFO treatment significantly decreased the half-life of Al in the rat brain. Desferrioxamine has been frequently used to diagnose and treat Al accumulation and toxicity (Yokel, 1994; Yokel et al., 1996). Significant reduction of Al accumulation and effective treatment of Al toxicity requires prolonged DFO therapy. The modest reduction in brain Al after ~108 DFO injections over 256 days in the present study is consistent with the clinical experience. Although DFO has been reported to reduce Al-associated neurobehavioral toxicity in the human (Yokel, 1994) and behavioral deficits in the rat and Al-induced neurofibrillary degeneration in the rabbit (Yokel et al., 1996), there have been no previous demonstrations of its ability to reduce brain Al. It is unclear whether DFO can cross the blood–brain barrier. Desferrioxamine may have promoted Al elimination from vascular and peripheral Al stores, thereby enhancing its redistribution out of the brain.

The hypothesized association of Al with Alzheimer’s disease and the known efficacy of DFO to promote Al elimination led to a 2-year study of DFO mesylate therapy: 125 mg (0.19 mmol) given im twice daily, 5 days weekly, for 2 years in Alzheimer’s disease patients (Crapper McLachlan et al., 1991). The DFO treatment reduced the rate of decline of daily living skills, compared to the lecithin placebo and no-treatment groups. There have been no subsequently reported studies that replicate or extend these observations. The effect of DFO might have been due to Al chelation. Alternatively, it may have resulted from Fe chelation and the associated reduction of Fe-induced oxidative injury. The present results suggest that prolonged DFO therapy might reduce brain Al in the human. These results further encourage follow-up study of the results reported by Crapper McLachlan et al. (1991).

This study replicated and expanded previous limited studies that showed entrance into the brain of a small fraction of Al after its oral or parenteral administration. Brain Al quantification for 256 days after its administration revealed Al persistence in the brain. This is consistent with limited reports from animals and humans suggesting one or more compartments with long Al half-lives. A long brain Al half-life, paired with continuous Al intake, can produce an age-related brain Al accumulation, as has been observed in the human. Long-term reduction of Al intake and/or enhancement of its excretion by Al chelation therapy should reduce the steady-state brain Al concentration.

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