Aluminum bioavailability from drinking water is very low and is not appreciably influenced by stomach contents or water hardness

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Abstract

The objectives were to estimate aluminum (Al) oral bioavailability under conditions that model its consumption in drinking water, and to test the hypotheses that stomach contents and co-administration of the major components of hard water affect Al absorption. Rats received intragastric 26Al in the absence and presence of food in the stomach and with or without concomitant calcium (Ca) and magnesium (Mg) at concentrations found in hard drinking water. The use of 26Al enables the study of Al pharmacokinetics at physiological Al concentrations without interference from 27Al in the environment or the subject. 27Al was intravenously administered throughout the study. Repeated blood withdrawal enabled determination of oral 26Al bioavailability from the area under its serum concentration time curve compared to serum 27Al concentration in relation to its infusion rate. Oral Al bioavailability averaged 0.28%. The presence of food in the stomach and Ca and Mg in the water that contained the orally dosed 26Al appeared to delay but not significantly alter the extent of 26Al absorption. The present and published results suggest oral bioavailability of Al from drinking water is very low, about 0.3%. The present results suggest it is independent of stomach contents and water hardness. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Aluminum (Al) is a neurotoxicant. It has been shown to play a role in the etiology of uremia- and dialysis-associated disorders of the brain (dialysis encephalopathy) and bone (aluminum-associated bone disease) (Alfrey et al., 1976;
Bushinsky, 1997). Al has been proposed as an environmental factor that may contribute to some neurodegenerative diseases, including Alzheimer’s disease (AD) (Cotton, 1994; Ferreyra-Moyano and Barragán, 1994). The role of Al in AD is controversial. Some studies have found an increase of Al in AD brain, others have not (reviewed in Yokel, 2000). Some epidemiological studies assessing the risk of dementia, including AD, have found a significant positive correlation between drinking water Al concentration and dementia (increased risk), whereas others have not (reviewed in Yokel, 2000).

The oral bioavailability of Al has been estimated in a number of studies. Some of the studies utilized conditions that model drinking water Al consumption (Hohl et al., 1994; Drüeke et al., 1997; Jouhanneau et al., 1997; Schönholzer et al., 1997; Priest et al., 1998; Stauber et al., 1999). These are briefly reviewed in the discussion. Conditions that model drinking water Al are twofold. One is the use of Al doses that reasonably compare with daily oral Al intake from water by humans, which is $\sim 1.5 \mu g$ Al/kg. This is based on consumption of 1.4 l per day of drinking water (US Environmental Protection Agency, 1997) containing 50–100 $\mu g$ Al/l (Letterman and Driscoll, 1988). The second condition is the introduction of Al as chemical species that might be found in drinking water or the use of water from a municipal water supplier. All of these studies estimated Al bioavailability based on urinary Al excretion. The extent of oral absorption (bioavailability) of hydrophilic substances is generally determined by a comparison of areas under the concentration (AUC) × time curve for the test substance given p.o. and i.v. (Riviere, 1999). This can be accomplished when the test substance is given as two analytically distinguishable, but not biologically different, forms at the same time by the p.o. and i.v. routes of administration. This was the method employed in the present study to address the first objective: to estimate the oral bioavailability of Al under conditions that model consumption of drinking water.

A second objective was to test the hypothesis that stomach contents inhibit oral Al bioavailability. Only one study compared oral Al bioavailability in fed versus fasted rats (Drüeke et al., 1997). However, they did not verify the absence of stomach contents at the time of oral Al dosing in the fasted rats.

Another variable that might influence Al absorption is the presence of Ca and Mg, the major cations constituting hard water. Water containing the equivalent of <75 mg/l of CaCO$_3$ is generally considered soft, whereas water with >150 mg/l of CaCO$_3$ equivalent is generally considered hard (Sawyer et al., 1994). An inverse relationship was observed when dietary Ca or intestinal perfusate Ca concentration were compared to gastrointestinal Al absorption or tissue Al concentrations (Feinroth et al., 1982; Provan and Yokel, 1990; van der Voet and de Wolff, 1998). Therefore, the third objective was to test the hypothesis that ‘hard’ water concentrations of Ca and Mg affect the bioavailability of ingested Al.

This study utilized $^{26}$Al, which was analyzed by accelerator mass spectrometry (AMS). The use of $^{26}$Al in the study of Al toxicokinetics has been reviewed (Flarend (Flack) and Elmore, 1998). As there is no measurable $^{26}$Al in the environment or in normal biological organisms, the interference of naturally occurring Al in the study of Al pharmacokinetics can be avoided. AMS measures the amounts of $^{26}$Al compared to $^{27}$Al. It is able to determine this ratio with a detection limit of $^{26}$Al/$^{27}$Al of $\sim 10^{-14}$. In the presence of 4 mg $^{27}$Al, as used in the present study, this represents $\sim 4 \times 10^{-17}$ g of $^{26}$Al, or $\sim 1 \text{ 000 000 atoms. Utilizing }^{26}\text{Al, pharmacokinetic studies of Al can be conducted at physiological concentrations. As there are negligible chemical differences between }^{26}\text{Al and }^{27}\text{Al they should be handled similarly in vivo. This presents the opportunity to concurrently administer the two Al isotopes and differentially analyze them in samples utilizing AMS for }^{26}\text{Al and electrothermal atomic absorption spectroscopy (ETAAS) for }^{27}\text{Al, when }^{26}\text{Al provides insignificant contribution to the total Al determined by ETAAS.}
2. Methods

2.1. Animals

The subjects were 21 male Fisher 344 rats, weighing 280 ± 42 gm (mean ± S.D.). Animal work was approved by the University of Kentucky Institutional Animal Care and Use Committee. The research was conducted in accordance with the Guiding Principles in the Use of Animals in Toxicology.

2.2. Experimental procedures

All rats were implanted with two femoral venous cannulae 1 day prior to oral dosing. This enabled i.v. administration through one cannula and blood withdrawal from another, to avoid contamination of withdrawn blood by the administered Al. The oral absorption of Al was determined in the unanesthetized rat. Blood was withdrawn 2, 1 and 0 h prior to, and 1, 2, 4, 8, 24, 48, 72, and 120 h after, oral dosing. The blood withdrawn, 0.3 ml in the first 6 samples, then 0.5, 2.1 and 2.1 ml in the 8, 24 and 72 h samples, was replaced by an equal volume of injected saline. Additionally, the rats had access to 2 ml water 2 h prior to dosing, they received the oral dose of $^{26}$Al in 1 ml water, and had free water access beginning 4 h after dosing. Serum was obtained for quantitation of $^{26}$Al and $^{27}$Al. Blood urea nitrogen (BUN) and creatinine were determined in the 120 h sample.

The subjects were randomly assigned to receive oral $^{26}$Al by gastric administration in the absence or presence of food in the stomach and in the presence of “soft” or “hard” water, in a $2 \times 2$ design. There were four or five rats/cell. The $^{26}$Al was provided by the Purdue Rare Isotope Measurement Laboratory (PRIME Lab), supplied as a 1 N HCl solution containing 149 nCi $^{26}$Al/g (7.8 μg/g) and 66 μg $^{27}$Al/g. This solution was diluted 100-fold with ultrapure water. Each rat received a 1 ml dose composed of 0.95 ml of this diluted solution containing 74.5 ng (1.41 nCi) $^{26}$Al and 625 ng $^{27}$Al, and 0.05 ml deionized water or aqueous solution of Ca and Mg carbonate, as appropriate. The pH of the administered solution was adjusted to ~5. Al can complex with inorganic and organic ligands, such as fluoride and fulvic acid. In their absence, as in the present study and in drinking waters that have little dissolved organic matter, Al primarily exists as soluble aluminum hydroxy aquo complexes (LaZerte et al., 1997).

The Al in the present study was predominantly in small molecular weight chemical species. All of the Al in the ‘soft’ water passed through 30 000 and 10 000 molecular weight cut-off (MWCO) membranes, whereas 34% passed through a 500 MWCO membrane. In similarly prepared ‘hard’ water, ~60% passed through 30 000 and 10 000 MWCO membranes and 34% through the 500 MWCO membrane.

Two control rats similarly received intragastric ‘soft’ water administration in the absence of food in the stomach. The solution was prepared as above, but contained no $^{26}$Al.

The absence of food in the stomach was produced by limiting food access to a 10% protein diet that was designed to minimize food retention in the stomach (Harlan Teklad 95215). This diet was available from 08:00 to 18:00 h daily for 5 days prior to the oral dosing. Food was removed 14 h before dosing and a fecal collection cup, modified from Wang and Peters (1963), installed to prevent fecal recycling (coprophagia). In a pilot study, six rats had access to this diet for 10 h daily for 7 days. Fourteen hours after diet removal, no food was found in their stomachs. Drinking water was freely available throughout the study except for the period from 14 h before to 4 h after oral dosing.

Food in the stomach at the time of Al dosing was produced by providing access to 1 g standard rat chow (Agway) and 2 ml of drinking water two hours before dosing. In a preliminary study, this produced an average of 1.7 g stomach contents. The Agway chow contained ~8.4 mM Al. This is ~325 times the amount of total Al in the oral dose. Assuming 0.3% Al absorption, based on the results of this study, this would contribute insignificant Al to systemic circulation compared to the ~28 μg Al infused hourly. All rats had access to 2 ml drinking water during the 2 h prior to intragastric dosing.
‘Hard’ water was produced by addition of CaCO₃ and MgCO₃ (70:30 ratio) to a final CaCO₃ equivalent of 300 mg/l. ‘Soft’ water had <10 mg/l CaCO₃ equivalent.

In a pilot study, five rats were prepared with a femoral and a jugular venous cannula. One day later, each was given an i.v. bolus injection of 2700 mgAl/kg, as AlK(SO₄)₂. Blood samples were obtained 2, 1 and 0 h prior to, and 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after, Al dosing. Serum was obtained, in which Al was quantitated by ETAAS. The results were analyzed, using RSTRIP (Fox and Lamson, 1989), to determine the systemic clearance (Cls) and steady state volume of distribution (Vd ss) of Al. These values were used to calculate a bolus and infusion of Al that was intended to achieve and maintain a serum Al concentration of ~700 µg/l.

The bolus dose was calculated as Vd ss × C ss, where C ss (the steady state serum Al concentration) was selected to be 700 µg/l. The infusion rate was calculated as Cls × C ss. The calculated i.v. injection dose was ~450 µg Al/kg and the infusion rate was 100 µg Al/kg/h. All 26Al-dosed rats received the calculated i.v. injection of 27Al 4 h prior to oral dosing and infusion of 27Al as AlK(SO₄)₂ from 4 h prior to 120 h after oral dosing.

2.3. Analysis of Al by electrothermal atomic absorption spectroscopy

Quality control samples were prepared by i.v. administration of 27Al to 2 rats. The rats were euthanized 24 h later, and exsanguinated. Aluminum was quantitated in five aliquots of serum by ETAAS, using a Perkin–Elmer 4100 ZL spectrometer. Serum samples were diluted tenfold with 0.2% HNO₃ containing 2.5 mM Mg as a matrix modifier, and compared to aqueous standards in the same matrix (10% rat serum plus HNO₃ and Mg). The values were 95, 115, 120, 128 and 141 µg Al/l; mean ± S.D. = 120 ± 17; relative standard deviation (RSD) = 14%. Within sample RSDs from repeated sample analyses were 0.5, 0.5, 7.7, 8.2 and 9.8%. These results demonstrated adequate analytical procedures. An aliquot of each serum obtained from the rats in this study was diluted at least 10-fold, as above, prior to analysis. All post-26Al-treatment serum samples were repeatedly analyzed until their total Al concentration RSD was <10%.

2.4. Analysis of aluminum-26 by accelerator mass spectrometry

Four mg 27Al (ICP/DCP standard, Aldrich) was added to an aliquot of each serum sample in a 7 ml Teflon screw cap container (Tuf-Tainer®). This represented >1 × 10¹⁰ as much added 27Al as the 26Al in the sample, and >1 × 10⁴ as much added 27Al as the 27Al in the sample. This enabled determination of the 26Al/27Al ratio by AMS. It also enabled quantitation of serum 26Al by its comparison to the known (added) 27Al concentration without significant contribution to the added 27Al from the 27Al in the serum sample. The sample was digested in 1 ml of a 70:30 HNO₃:H₂O₂ v/v mixture. The liquid was evaporated, as described by Yokel and Melograna (1983), and the residue ashed at 1000°C. The radionuclide (26Al) to stable nuclide (27Al) ratio was determined by the PRIME Lab (Sharma et al., 2000) to a precision of <10% error. One value with an error of 17% was not included in the reported results. Five replicate sera prepared by this method had a RSD of 4.3%. Aliquots of these replicate sera that were processed with samples of serum obtained after 26Al dosing were within 10% of the mean and were within the range of the five replicates.

2.5. Data analysis

A criterion for acceptance of post-treatment serum 26Al concentrations considered to be reliably above pre-treatment serum values was established as >2 S.D. above the mean pre-treatment serum 26Al concentration. This criterion was >6 fg 26Al per ml. Values below this criterion are not presented graphically and were not used in the data analysis. This criterion was met by all of the samples obtained from 1 to 24 h, 3 of the 72 h but none of the 120 h serum samples. The mean half-life of elimination of the 26Al was <6 h. Therefore, blood was obtained for ~4 half-lives, which is more than sufficient time to determine
the AUC of the $^{26}$Al. Each subject’s pre-treatment serum $^{26}$Al concentration was subtracted from its post-treatment values. Oral $^{26}$Al bioavailability was calculated using the following equation:

$$\frac{\text{The sum of the trapezoidal areas for } ^{26}\text{Al}}{\text{Mean } ^{27}\text{Al serum concentration for the same time period} \times \frac{\text{27Al infusion rate}}{\text{26Al dose}}}. $$

A two-way ANOVA was used to test for significant treatment differences.

3. Results

The results obtained from the 5 rats given an i.v. injection of 2700 µg $^{27}$Al/kg in the pilot study were best fit by two exponents. The $\text{Cl}_s$, based on integrals to the last time point, was $145 \pm 60 \text{ ml/h/kg (mean \pm S.D.)}$. The $\text{Vd}_{ss}$ was $0.65 \pm 0.37 \text{ l/kg}$. These values were used to calculate the $^{27}$Al bolus dose and infusion rate in the main study of this report, the estimation of oral Al bioavailability after $^{26}$Al oral dosing.

The BUN and serum creatinine values of the rats that received oral $^{26}$Al and i.v $^{27}$Al dosing ranged from 10 to 28 and from 0.3 to 0.5 mg/dl, respectively. They were within normal limits (<30 and 1 mg/dl, respectively).

The $^{26}$Al concentration in the serum samples obtained from all rats prior to $^{26}$Al (or $^{26}$Al vehicle) dosing ranged from 0 to 8.4 (mean = 1.6) fg/ml. The concentration of $^{26}$Al in the 11 samples from the two non-$^{26}$Al-treated rats after vehicle dosing ranged from 0 to 1.2 fg/ml (mean = 0.4). Peak serum $^{26}$Al concentration after oral $^{26}$Al dosing ranged from 249 to 1271 fg/ml. Therefore, the oral $^{26}$Al dose increased peak serum $^{26}$Al ~115- to 800-fold above mean pre-treatment values. The time courses of serum $^{26}$Al following oral $^{26}$Al dosing for the four treatment groups are shown in Fig. 1.

The results for the four treatment groups are shown in Table 1. Neither the presence of food in the stomach or concomitantly administered Ca and Mg, modeling ‘hard’ water, significantly affected oral Al bioavailability. Overall, oral Al bioavailability averaged 0.28% (95% C.I. = [0.19–0.36]).

Peak serum $^{26}$Al concentration was seen in the 1 h sample in four of the five rats in the No food in stomach, ‘soft’ water group. The peak was at 2 h in the fifth rat, resulting in a mean peak time of 1.2 h. The presence of Ca and Mg in the water increased the mean time to peak serum $^{26}$Al concentration to 2 h, as did the presence of food. Peak serum $^{26}$Al concentration was seen in the 1 h sample in one rat, the 2 h sample in two rats, and the 4 h sample in two rats in the presence of both Ca and Mg in the water and food in the stomach (Food in stomach, ‘hard’ water group). This resulted in a mean of 2.6 h to peak serum $^{26}$Al concentration. RSTRIP analysis of mean residence times also revealed a retardation of the Al absorption rate in the No food in stomach, ‘hard’ water group to 118% of that seen in the No food in stomach, ‘soft’ water group. The presence of food increased the mean residence time to 124% and the presence of Ca and Mg as well as food increased to time to 185% of the No food in stomach, ‘soft’ water group.

4. Discussion

The estimate of Al oral bioavailability in this study (0.28%) was moderately higher than some previous reports. Oral Al bioavailability estimates of ~0.06–0.1% were reported in studies conducted in rats utilizing $^{26}$Al. These estimates were based on Al in urine within 5 h after Al(OH)$_3$ or Al-maltolate dosing (Schönholzer et al., 1997); the sum of cumulative 30 day urinary Al excretion and the Al retained in bone, liver and brain (Jouhanneau et al., 1997); or urinary Al excretion in 48 h plus skeletal Al (Driëke et al., 1997). Some of these studies had only a few subjects. In a study that included 21 humans, Stauber et al. (1999) estimated the oral bioavailability of $^{27}$Al, present in water from a municipal water treatment facility, to be 0.36%. Two studies, each conducted in two humans and utilizing $^{26}$Al, estimated oral Al bioavailability to be 0.1 and 0.22%, respectively (Hohl et al., 1994; Priest et al., 1998). All of these studies determined oral Al absorption based
Fig. 1. Concentration of $^{26}$Al in serum versus time after oral administration of $^{26}$Al in water in the absence or presence of food in the stomach and in the absence (soft) or presence (hard) of 300 mg CaCO$_3$/l equivalent in the water. The values are mean ± S.D. from (5) rats, except for the food in stomach, ‘soft’ water group, where $n = 4$.

on urinary Al excretion, although a few based the estimate on selected tissue Al plus urinary Al excretion. Urinary Al excretion can underestimate Al absorption, since it does not account for the fraction of Al eliminated by other routes, although small, and the Al that is retained during the duration of the study. Only Priest et al. (1998) and Stauber et al. (1999) attempted to correct their estimate of Al oral bioavailability for the fraction of absorbed Al that was not thought to be excreted in the urine during the duration of their studies.

Previous studies (cited above) and the present results show that Al oral bioavailability is very low. The poor oral bioavailability contributes to greater relative variability in the estimates of its absorption than would be expected with substances that are more efficiently absorbed. With one exception, none of the studies cited above reported a measure of the variability of their estimate of oral Al bioavailability. Driese et al., 1997 found $0.036 ±$

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<th>No food in stomach</th>
<th>Food in stomach</th>
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<td>Soft water</td>
<td>$0.23 ± 0.12 (5)$</td>
<td>$0.21 ± 0.20 (4)$</td>
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<tr>
<td>Hard water</td>
<td>$0.24 ± 0.16 (5)$</td>
<td>$0.41 ± 0.20 (5)$</td>
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* Values are mean ± S.D. from ($n$) rats, expressed as a percentage.
0.019% (mean ± S.D.) of the administered $^{26}$Al in urine and 0.025 ± 0.013% in bone of 8 rats.

The use of $^{26}$Al enables determination of Al oral bioavailability at Al concentrations relevant to drinking water. An added strength of the present study is the concurrent use of two isotopes of Al to determine oral Al bioavailability by comparison of the AUCs of an oral, $^{26}$Al, and an i.v., $^{27}$Al, form of Al in the same subject at the same time. A disadvantage of this approach is the high cost of $^{26}$Al analysis by AMS. Financially, practical studies are limited to fewer samples than studies utilizing less expensive analytical methods. For substances such as Al that have very low oral bioavailability, it is difficult, without a large number of subjects, to detect small differences in the percentage absorbed that might be produced by variables such as stomach contents. To estimate the power of the present study, a two-way ANOVA was used to determine whether the main effects of food in the stomach (absence vs. presence), water condition (soft vs. hard) or the interaction between these two main effects were related to oral aluminum bioavailability. If the effect sizes of the main effect and interaction terms had been on the order of 0.45–0.6, the power of the F test to detect significant factors would have been 80–90%. However, the observed effect sizes were on the order of 0.06–0.09, so the power was in the 15–25% range. To put this into context, if two-sample $t$-tests had been used to assess a significant effect of either food versus no food or soft versus hard water, the magnitude of the difference between food versus no food or between soft versus hard water would have had to have been on the order of 250–260%. The observed differences were 37–48%. Therefore, the relatively small sample size, which was a product of the high cost of $^{26}$Al analysis, and the variability, which is a result of the very low oral bioavailability of Al, limited the power of the study. Significant differences could have been detected only if there was an approximate threefold difference between the no food versus food groups or the soft versus hard water groups. Given the very low oral bioavailability of Al, changes in oral absorption of a few fold would not greatly influence the contribution of Al in drinking water to the human Al body burden.

Oral bioavailability of lead, mercuric mercury and perhaps manganese is greater in immature than mature mammals (ATSDR, 1997). This is an important issue for risk assessment. The age-related dependence of Al absorption was not addressed by ATSDR (1999). It cannot be addressed from the results of the present study as only adult rats were studied. At this time there is no good data under conditions that model consumption of drinking water to indicate whether or not oral Al bioavailability is age-dependent.

We did not find support for the hypothesis that food in the stomach significantly influences Al bioavailability from water, although stomach contents delayed Al absorption. Some of the studies of oral Al bioavailability that model Al exposure from drinking water restricted food access, whereas others did not. Schönholzer et al. (1997) and Dru¨eke et al., (1997) dosed rats after a 16 or 24 h fast, whereas Jouhanneau et al. (1997) and Dru¨eke et al. (1997) estimated oral Al bioavailability in the presence of free food access. The subjects in the study of Stauber et al. (1999) consumed a standard diet, whereas the two subjects in the study of Priest et al. (1998) were fasted overnight. Except for a group of fasted rats (Dru¨eke et al., 1997), oral Al bioavailability estimates ranged from 0.06 to 0.36% in these studies. Oral Al bioavailability in 24 h food deprived rats was 0.94% (Dru¨eke et al., 1997), providing the only other direct assessment of the effect of stomach contents on oral Al absorption. However, rats recycle their feces. We (unpublished results) and others (Walton et al., 1995) have found stomach contents in rats deprived of food for 24 h or longer. Therefore, the absence of stomach contents cannot be assured in the rats of the study of Dru¨eke et al. (1997). Overall, there is little evidence, other than the study of Dru¨eke et al. (1997) that food in the stomach significantly affects the extent of oral Al absorption. The present results do not support this notion. Therefore, the possible presence of feces in the stomach in some of the previously conducted studies may not have influenced oral Al bioavailability.

The suggestion of delayed Al absorption in the presence of stomach contents in the present study is consistent with the apparent site of Al absorp-
tion, the upper intestine. Al would be expected to exist primarily as the free ion with associated waters of hydration within the stomach in the absence of stomach contents, due to the low pH. Absorption by diffusion from the stomach would not be predicted. Uptake into stomach sacs was found to be much less than into small bowel and colon (Whitehead et al., 1997). Concurrently administered Al and glucose rapidly appeared in the blood and reached peak concentrations about the same time, suggesting that the site of Al absorption is probably the proximal small intestine (Fro-ment et al., 1989; Nagy and Jobst, 1994). Although the presence of stomach contents appeared to delay Al absorption in the present study, it did not significantly effect the percentage of Al that was absorbed under conditions that model human consumption of drinking water.

We did not find evidence that a high cation content in water influences oral Al bioavailability, although it delayed Al absorption. This is the first report to directly assess the effect of water hardness on Al absorption. The lack of effect of Ca and Mg on the extent of oral Al absorption is not in agreement with some indirect studies of an inverse relationship between Ca presence or Ca status and Al absorption, as reviewed in the Introduction. Wills et al. (1993) found no significant difference in brain, bone or spleen Al concentrations in rabbits that consumed Al in hard versus soft water for 1 year, while consuming a normal diet. The delay of Al absorption in the presence of Ca and Mg at a final CaCO₃ equivalent of 300 mg/l that was observed in the present study suggests competition between the absorption of Al and Ca and/or Mg. This is consistent with the conclusion of van der Voet and de Wolff, 1998 that ‘… Al attempts to mimic Ca in its Na-related intestinal passage.’ Unfortunately, all of these previous studies were conducted at much higher Al concentrations, which do not model drinking water consumption. It is possible that prolonged Ca or Mg exposure initiates processes that modify Al absorption. Some of the previously conducted studies utilized prolonged exposure to an altered Ca concentration (Provan and Yokel, 1990; Wills et al., 1993) whereas others studied the effects of acute exposure to varying Ca concentrations (Feinroth et al., 1982; van der Voet and de Wolff, 1998), preventing resolution of this issue. Based on ionic radii, Macdonald and Martin (1988) suggested that it is more likely that Al and Mg would compete in biological systems than would Al and Ca. Although there is some evidence for Al–Mg competition in vivo, there are no reports of the affect of Mg on Al absorption. Although the present results suggest that Ca and/or Mg retard Al absorption, they did not significantly effect the percentage of Al absorbed under conditions that model human consumption of hard drinking water.

The results of the present study, along with previous estimates of oral Al bioavailability under conditions that model human consumption of drinking water, suggest that Al bioavailability from drinking water is in the range of 0.25–0.4%. The present results suggest that this is not greatly influenced by either the presence of food in the stomach or water hardness.

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