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Aluminum bioavailability from tea infusion

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Abstract

The objective was to estimate oral Al bioavailability from tea infusion in the rat, using the tracer ^{26}Al. ^{26}Al citrate was injected into tea leaves. An infusion was prepared from the dried leaves and given intra-gastrically to rats which received concurrent intravenous ^{27}Al infusion. Oral Al bioavailability (F) was calculated from the area under the ^{26}Al, compared to ^{27}Al, serum concentration × time curves. Bioavailability from tea averaged 0.37%; not significantly different from water (F = 0.3%), or basic sodium aluminum phosphate (SALP) in cheese (F = 0.1 to 0.3%), but greater than acidic SALP in a biscuit (F = 0.1%). Time to maximum serum ^{26}Al concentration was 1.25, 1.5, 8 and 4.8 h, respectively. These results of oral Al bioavailability × daily consumption by the human suggest tea can provide a significant amount of the Al that reaches systemic circulation. This can allow distribution to its target organs of toxicity, the central nervous, skeletal and hematopoietic systems. Further testing of the hypothesis that Al contributes to Alzheimer's disease may be more warranted with studies focusing on total average daily food intake, including tea and other foods containing appreciable Al, than drinking water.

Keywords

Accelerator mass spectrometry; Aluminum; Atomic absorption spectrometry; Oral bioavailability; Rat; Tea beverage

Introduction

Aluminum (Al) can produce toxicity to the central nervous, skeletal and hematopoietic systems. It can produce an encephalopathy in renal-impaired humans (dialysis encephalopathy), cognitive deficits in young children, a low-turnover bone disease, and a microcytic hypochromic anemia. It has been controversially implicated as an environmental factor that may contribute to some neurodegenerative diseases, including Alzheimer's disease (AD) (Krewski et al., 2007; Sjögren et al., 2007). The primary dietary source of Al in the U.S. for the typical human is foods and beverages, including tea. Average daily Al intake is typically

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5 to 10 mg (Pennington and Schoen, 1995). Drinking water provides ~ 0.1 mg of Al (~ 1.5% of total daily dietary Al intake) whereas in countries where Al from other sources is relatively small and tea consumption relatively large, as in the UK, tea may contribute up to 50% of total daily Al intake (UKMAFF, 1993). In a defined diet study conducted in Australia to estimate oral Al absorption, instant tea provided 1.8 mg Al/l, > 50% of the 3.2 mg Al consumed daily (Stauber et al., 1999). Tea infusions typically contain 2 to 4 mg Al/l (Sepe et al., 2001; Flaten, 2002). Herbal tea infusions contain less Al (Hayacibara et al., 2004). Antiperspirants, vaccines, allergy desensitization injections and Al-based oral anti-acids can contribute significant amounts to total human Al exposure in some people (Yokel and McNamara, 2001; Yokel, 2004; Krewski et al., 2007).

Oral bioavailability (fractional absorption) is the amount absorbed compared to the amount administered. Oral Al bioavailability has been estimated in a number of studies, reviewed by Yokel and McNamara (2001) with more recent studies reported by Steinhausen et al. (2004) and Zhou et al. (2008). Because it was suggested that Al bioavailability from water is greater than from food (Martyn et al., 1989), the primary interest has been to model drinking water Al consumption. The greater bioavailability was attributed to organic ligands in food, such as phytates and polyphenols, that were suggested to complex Al and inhibit its oral absorption (Reto et al., 2007). Determination of oral Al bioavailability from food is complicated by the many different types of available foods, and their different methods of preparation, including ingredients. Organic ligands bind > 90% of Al in tea (Gardner and Gunn, 1995). Their identity has not been determined, although polyphenolic and oxalate complexes have been suggested (Flaten, 2002).

Oral aluminum bioavailability has been estimated using several methods. These were reviewed and critiqued by Yokel and McNamara (Yokel and McNamara, 2001). The standard method to determine oral bioavailability is the comparison of areas under the plasma/serum concentration-time curve after po and iv administration in the same subjects (Rowland and Tozer, 1995; Bauer, 2006). The po and iv doses can be administered concurrently when the test substance is given as two analytically distinguishable, but biologically indifferent, chemical species. In this study, the use of ^{26}Al, which is not present in the environment or in normal biological organisms, was incorporated as a tracer in the oral dose (tea infusion). The use of ^{26}Al to study Al toxicokinetics was reviewed (Flarend and Elmore, 1998). ^{26}Al was analyzed by accelerator mass spectrometry (AMS), which measures the ^{26}Al/^{27}Al ratio with a detection limit of ~ 1,000,000 ^{26}Al atoms. The use of ^{26}Al enables the conduct of physiologically-relevant pharmacokinetic studies of Al. ^{27}Al was concurrently administered as the iv dose. Electrothermal atomic absorption spectrometry was utilized to quantify total Al, essentially the ^{27}Al from its iv administration because the concentration of ^{27}Al was orders of magnitude greater than ^{26}Al. This method was used to address the objective of the present study; to estimate oral Al bioavailability from tea infusion in the rat.

Methods

Materials

^{26}Al was provided by the Purdue Rare Isotope Measurement Laboratory (PRIME Lab). It was supplied as 16.5 nCi (865 ng) ^{26}Al/ml and with a 34:1 ^{27}Al:^{26}Al ratio (30.3 μg total Al/ml) in 0.01 N HCl.

Hydroponic studies were conducted in collaboration with Dr. Jack Buxton, Department of Horticulture, University of Kentucky, to incorporate Al into the spinach plant in the same chemical species as it is present *in situ*. We were not able to produce sufficient Al loading for an oral bioavailability study. It was concluded that this approach would not be practical for the tea plant (*Camellia sinensis*). Therefore, Al was injected into the central vein at the base of the

tea leaf. Al was injected as the citrate because Al taken up from the soil was shown to be associated with charged organic compounds present in symplasm, predominantly citrate (Kochian and Jones, 1997) and Al citrate added to nutrient solution was transported from plant roots to the upper part of plants unchanged (Polak et al., 2001). In preliminary studies using ^{27}Al, we found 85% of the Al infused into the base of the tea leaf to be taken up from the central vein into the leaf. When powdered leaf was placed in boiling water, 77% of the Al was recovered in the infusate.

To prepare a tea infusion containing ^{26}Al, 3 ml of ^{26}Al solution, containing 50 nCi (2620 ng) ^{26}Al, and 90,000 ng ^{27}Al, were dried to a powder to which was added 96.9 µl 1M Al and 300 µl 1M citrate and pH adjusted to 3.11 to optimize Al citrate formation. Speciation calculations suggested >> 99% of the Al would be associated with citrate; 45% as Al(citrate)$_2$, 30% as $Al_3(H_{-1}citrate)_3(OH)$, 14% as $Al_2(H_{-1}citrate)_2$, 9% as Al(citrate), < 0.002% as free Al and the remainder other Al citrate species (personal communication from Dr. Wesley Harris, University of Missouri-St. Louis). One hundred µl was infused over 10 h into the base of each of four tea leaves. Total Al in the 100 µl was 0.65 mg, delivering the same amount of Al as is inherently in tea leaves (0.5 to 1 mg/gm). The central vein of each leaf was dissected out and the remainder dried overnight at 70 °C. The leaves (totaling 1.1 g dry weight) were ground to a powder in a coffee grinder and transferred into an emptied commercial tea bag. To maximize Al extraction the bag was placed in 20 ml of boiling MilliQ water in a 50 ml plastic tube, gently agitated and allowed to steep for 30 minutes. The fluid was squeezed from the bag into the infusate, which was refrigerated. Fine particles were allowed to settle and the supernatant removed and divided into 1 ml aliquots that were frozen until the day of dosing to rats. A similar tea infusate was prepared without ^{26}Al by similarly infusing tea leaves with non-^{26}Al containing Al citrate and preparation of an infusion by steeping 500 mg of tea in 10 ml water. It was administered to a sentinel rat to document sample contamination.

The ^{26}Al concentration in the tea infusion was determined. Five samples of the tea infusion dosing material (mean ± S.D., 20.9 ± 3.4 mg) were diluted 4 times, each a 10-fold dilution, serially, with MilliQ water. One ml was transferred to a porcelain crucible to which 4 mg Al (Aldrich ICP/DCP standard) was added. The samples were dried over night then slowly heated to 1000 °C in a muffle furnace to convert the Al to Al oxide, which was analyzed by accelerator mass spectrometry. The tea infusion was found to contain 1.36 nCi (71.3 ng) ^{26}Al/ml.

Animals

The subjects were 9 male Fisher 344 rats, weighing 312 ± 5 g (mean ± SD). They were housed in the University of Kentucky Division of Laboratory Animal Resources facility at 30–70% humidity and 65–75° F. 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. Eight of the nine rats were given an intra-gastric administration of tea infusion containing ^{26}Al. One sentinal rat was given an intra-gastric administration of tea infusion not containing ^{26}Al, to document sample contamination.

Experimental procedures

The rats were acclimated to a 10% protein diet designed to minimize food retention in the stomach (Harlan Teklad 95215). It contained 10 ± 0 mg Al/kg (triplicate analysis). They had free food access from 08:00 to 18:00 h daily for ≥ 5 days prior to the determination of oral Al bioavailability. This diet was shown to result in the absence of food in the stomach 14 h after its withdrawal when fecal recycling (coprophagia) was prevented by a fecal collection cup, as described by Yokel et al. (2001). Deionized drinking water was freely available throughout the study except for the period from 14 h before to 4 h after oral dosing. It contained 5 µg Al/l.

The rats were implanted with two femoral venous cannulae 1 day prior to intra-gastric administration of oral tea infusion. This enabled iv administration of ^{27}Al through one cannula and blood withdrawal from another, to avoid contamination of withdrawn blood by the administered Al.

The rats were randomly assigned to be given 1 ml of tea infusion containing ^{26}Al (n = 8), in the absence of food in the stomach, or similarly dosed with tea infusion containing no ^{26}Al (n = 1). Quantification of tea infusion delivery was determined by weighing the solution in a microtube. It was delivered intra-gastrically to the rat via gavage needle. Oral bioavailability calculations were based on the weight of administered tea infusion.

Oral Al bioavailability was determined in the un-anesthetized rat. Based on the results of a pilot study, the rats were iv infused at 100 μg Al/kg/h to produce an estimated 500 μg Al/l in blood plasma for the ^{27}Al dose, as described by Yokel et al. (2001). In this study $AlK(SO_4)_2$ was continuously infused from 14 h prior to 60 h after oral dosing. Blood was withdrawn immediately before and 1, 2, 4, 8, 24, 36, 48 and 60 h after oral dosing. These sample times were based on two similar studies in which rats were given oral Al solution. In the initial study blood samples were obtained to 120 h after administration of ^{26}Al in water. However, the ^{26}Al in only two samples beyond 24 h met the criteria to be reliably above pre-treatment serum values. Therefore, the results were essentially based on samples up to 24 h, as described by Yokel et al. (2001). In the second study in which ^{26}Al was given in water in the presence of various ligands, blood samples were obtained to 24 h (Zhou et al., 2008). The sampling times of the present study included 36, 48 and 60 h, to enable comparison to two other similarly-conducted studies in which ^{26}Al was incorporated into foods, and to assure sufficient time for total Al absorption (Yokel and Florence, 2006; Yokel et al., 2008). The blood withdrawn (0.3 ml for the 0 to 4 h samples, 0.5 ml for the 8 h sample, 2.1 ml at 24 h, 3.1 ml at 36 h, and 4.1 ml at 48 h), was replaced by an equal volume of injected saline. Additionally, the rats had free access to water and food (Harlan Teklad 95215 diet) beginning 4 h after dosing. The 60 h blood sample was obtained by anesthetizing the rat and exsanguination from a femoral cannula and then the heart. Serum was obtained for ^{26}Al and ^{27}Al analysis. Blood urea nitrogen (BUN) and serum creatinine were determined in the 60 h sample.

Preparation and analysis of total Al by electrothermal atomic absorption spectrometry

The procedures were as recently described by Yokel and Florence (2006).

Preparation and analysis of ^{26}Al by accelerator mass spectrometry

The procedures were as described by Yokel et al. (2001).

Data analysis

A criterion for acceptance of post-treatment serum ^{26}Al concentrations considered to be reliably above pre-treatment serum values was established as > 2 SD above the mean pre-treatment serum ^{26}Al concentration. This criterion was 2 pg ^{26}Al/l. 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 in the ^{26}Al-dosed rats except one value at 60 h. The results were analyzed using the pharmacokinetic-pharmacodynamic modeling and analysis program WinNonLin, using non-compartmental analysis (Pharsight, 2008). Each rat's pre-treatment serum ^{26}Al concentration was subtracted from its post-treatment values. Oral ^{26}Al bioavailability (F) was calculated as follows and expressed as a percent:

$$F=\frac{\text{The sum of the trapezoidal areas for } ^{26}\text{Al}}{\text{The sum of the trapezoidal areas for } ^{27}\text{Al}} \times \frac{^{27}\text{Al hourly infusion rate} \times \text{time}}{^{26}\text{Al dose}}$$

Time to maximum serum ^{26}Al concentration (T_{max}) and the maximum concentration (C_{max}) were calculated using WinNonLin. Kruskal-Wallis tests and Dunn's multiple comparison tests (when the Kruskal-Wallis test was significant) were used to test for differences in the oral bioavailability, T_{max}, and C_{max} of Al from the tea infusion compared to results previously obtained using the same procedure: 1% and 2% acidic SALP in a biscuit (Yokel and Florence, 2006), 1.5 and 3% basic SALP in a cheese (Yokel et al., 2008), and from water (Yokel et al., 2001; Zhou et al., 2008). This test was used because the results had significantly different variances. $P < 0.05$ was accepted as statistically significant.

Results and Discussion

Each rat received 1.37 ± 0.2 nCi ^{26}Al in the tea infusion. Each rat's serum ^{26}Al results were normalized to its ^{26}Al dose. The BUN values ranged from 7.6 to 15.1 mg/dl and the serum creatinine values were ≤ 0.2 mg/dl, well within normal limits (< 30 and 1 mg/dl, respectively).

Pre-dosing serum ^{26}Al ranged from 0.1 to 2.4 (mean ± S.D. 0.62 ± 0.73) pg/l. Only 1 of the 8 samples from the non-^{26}Al-dosed rat exceeded the criterion for acceptance of post-treatment serum ^{26}Al concentrations, indicating no appreciable cross-contamination. Peak serum 26Al concentrations after oral 26Al dosing in tea ranged from 326 to 962 pg/l. The oral ^{26}Al dose increased peak serum ^{26}Al 525- to 1550-fold above mean pre-treatment values. The time course of serum ^{26}Al following oral ^{26}Al dosing is shown in Figure 1. Peak serum ^{26}Al concentration occurred in the 1 h sample in 6 rats and the 2 h sample in 2 rats. As the mean terminal half-life of ^{26}Al elimination was 10.4 ± 1.8 h blood was obtained for > 3 half-lives; more than sufficient time to determine the area under the ^{26}Al (concentration×time) curve (AUC). The $AUC_{time\ to\ last\ sample}$ was ≥ 97.9% $AUC_{infinity}$ in all cases, indicating that samples were collected for sufficient time to adequately determine oral Al absorption. Oral bioavailability results are shown in Table 1. Oral Al bioavailability from the tea infusion was greater than previously observed from water and two representative foods containing the food additive SALP in studies that used the same methods. This difference reached statistical significance only for Al incorporated into acidic SALP in a baked good. T_{max} and C_{max} of the tea infusion (Table 1) were not different from water, but were significantly less and greater, respectively, from the combined 1% and 2% acidic SALP in biscuit and 1.5 and 3% basic SALP in cheese results. Al from the tea infusion was rapidly absorbed, comparable to that seen from water (Figure 1 compared to Figure 2). The T_{max} of Al from tea infusion is consistent with the apparent site of Al absorption, the upper intestine (Froment et al., 1989).

The typical tea bag contains 2 g of finely ground tea. The dry tea leaf used to prepare tea beverage often contains 500 to 1000 mg Al/kg (Scancar et al, 2003), Many studies have shown that 20 to 35% of the Al in tea leaves is solubilized into the first infusion when the beverage is prepared, with decreasing amounts in subsequent infusions, e.g. (Wang et al., 1994).

No prior studies adequately determined oral Al absorption from tea beverage. Fujii et al. (2002) gave Oolong tea infusion or Al citrate (16.7 ml/kg of 11.9 mg Al/l; 0.2 mg Al/kg), or water, to rats. Blood samples were obtained 0.5, 1, 2 and 3 h later. The serum Al AUC was 4-fold greater for Al citrate than for Oolong tea. These authors also gave rats 15 ml/kg of Oolong, green or black tea, containing 11.9 ppm (mg/l) Al (0.18 mg Al/kg), or water (Fujii et al., 2002). The AUCs for Al for green and black teas were 238 and 86% of those seen for Oolong tea, suggesting greater relative Al bioavailability from green than Oolong or black teas. However, oral Al bioavailability cannot be calculated from these results because they lack the AUC following iv administration (Bauer, 2006).

Increased urinary Al concentration was seen in 6 humans in the 12 h after consumption of 1.2 l of tea compared to water (Koch et al., 1988). The authors did not report urine volume. If urine

volume was comparable after tea and water consumption, as reported by Powell et al. (1993), urinary Al output was greater following tea, suggesting Al absorption from tea. In one subject total 24 h urinary Al output was 0.02 mg after consumption of 2 l of tea containing 5.9 mg Al compared to 0.004 mg Al in the urine after consumption of 2 l of water (Powell et al., 1993). They did not calculate oral Al bioavailability from their results. Their results suggest 0.27% Al bioavailability from tea, based on calculations conducted by one of the authors of the present report. In another study, 4 humans who consumed 2 l of tea containing 8 mg Al eliminated an average of 0.003 mg Al within the subsequent 7 h in their urine (Gardner and Gunn, 1995). The authors did not calculate oral Al bioavailability from their results. Their results suggest 0.04% Al bioavailability from tea, based on calculations conducted by one of the authors of the present report. However, Gardner and Gunn (1995) only collected urine for 7 h after tea consumption. Seven h is not sufficient time to accurately determine total Al output from the Al consumed in the tea. In the human, only 62% of Al eventually excreted in the urine appeared within the first 24 h (Priest et al, 1996). Therefore, 0.04% would be an underestimate of oral Al bioavailability from tea. (Wu et al., 1997) reported the results of a study in four humans who consumed 0.9 l of tea prepared from Oolong or Long-Jin (green) tea, containing 3.68 and 1.14 mg Al. They reported 24 h urine Al output from which one of the authors of the present report calculated that 0.5 and 1.05% of the ingested Al was excreted in their urine in the subsequent 24 h, above urine Al excretion after consuming water, assuming no changes in dietary Al intake.

This report describes the first adequately designed study to determine the oral bioavailability of Al from tea. This study utilized eight rats, whereas the three prior studies from which one can estimate oral Al bioavailability from tea employed 1, 4 and 4 humans. We followed Al for 60 h after its administration *vs*. 7 to 24 h in the prior studies. ^{26}Al was utilized as a tracer, as described by Yokel et al. (2001), providing a less ambiguous estimate of oral Al absorption due to its lack of presence in the environment and rats in the absence of its administration. Studies with ^{27}Al have the problem of differentiating administered from background ^{27}Al. The results calculated from one human (Powell et al., 1993) followed for 24 h and four humans followed for 24 h (Wu et al., 1997), in which urinary Al excretion was used to estimate Al absorption, given the limitations of that method, are reasonably consistent with the present results that suggest oral Al bioavailability from tea beverage is 0.37%.

In recent years, a number of studies have been conducted to address the hypothesis that Al in drinking water contributes to AD (Krewski et al., 2007). Many showed a significantly higher incidence of AD among people living in districts that had more Al in the drinking water than in people drinking water that contained less Al (Krewski et al., 2007). To characterize the risk of Alinduced adverse health effects from Al exposure in drinking water, (Krewski et al., 2007) determined the margin of exposure (MOE; ratio of the exposure level of concern to the exposure level) for neurological endpoints (e.g. AD) in relation to oral Al exposure from drinking water. The results revealed a MOE ≥ 1, suggesting the neurological (AD) health endpoint associated with oral Al exposure deserves scrutiny. Given the potential high Al concentration in tea beverage, considerable consumption of tea by some people, and oral bioavailability of Al from tea that is at least as great as from water, the relative source contribution from tea beverage should be considered with heightened concern. If drinking water presents health risks from Al exposure, one would anticipate tea to do so to a greater extent. In fact, three studies have shown a non-significantly greater odds ratio for AD in those who consume more tea (Broe et al., 1990; Anonymous, 1994; Forster et al., 1995), whereas one study found a non-significantly lower odds ratio (Rogers and Simon, 1999). Further testing of the hypothesis that Al contributes to AD may be more warranted with studies focusing on total daily food intake, including tea consumption and other foods containing appreciable amounts of Al, than drinking water.

In summary, oral Al bioavailability from tea was 0.37%. Studies using the same methods showed 0.28 and 0.29% of Al was orally absorbed from water (Yokel et al., 2001; Zhou et al., 2008). Given that oral Al bioavailability from tea was not significantly different from water and tea contains much more Al than water, tea contributes more Al than does water to the body burden of tea drinkers. It has been cautioned that the potential for Al toxicity from drinking tea should not be overlooked, particularly among people who consume considerable tea that has a high Al content, as occurred among some people in China who consume poor quality tea made from older leaves and branches (Wong et al., 1998). The present results suggest that, among foods and beverages, tea can be a significant contributor to systemic Al.

Abbreviations

AD, Alzheimer's disease; Al, aluminum; AUC, area under the (concentration×time) curve; C_{max}, maximum serum concentration; F, oral bioavailability; SALP, sodium aluminum phosphate; T_{max}, time to maximum serum concentration.

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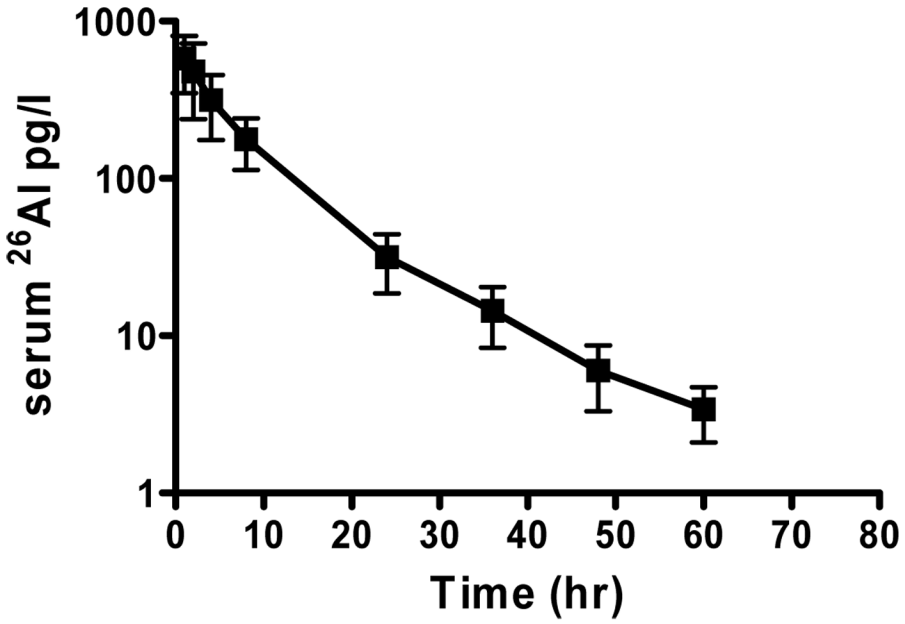

Figure 1.
Concentration of ^{26}Al in serum versus time after consumption of ^{26}Al in a tea infusion. The values are mean ± SD from 8 rats.

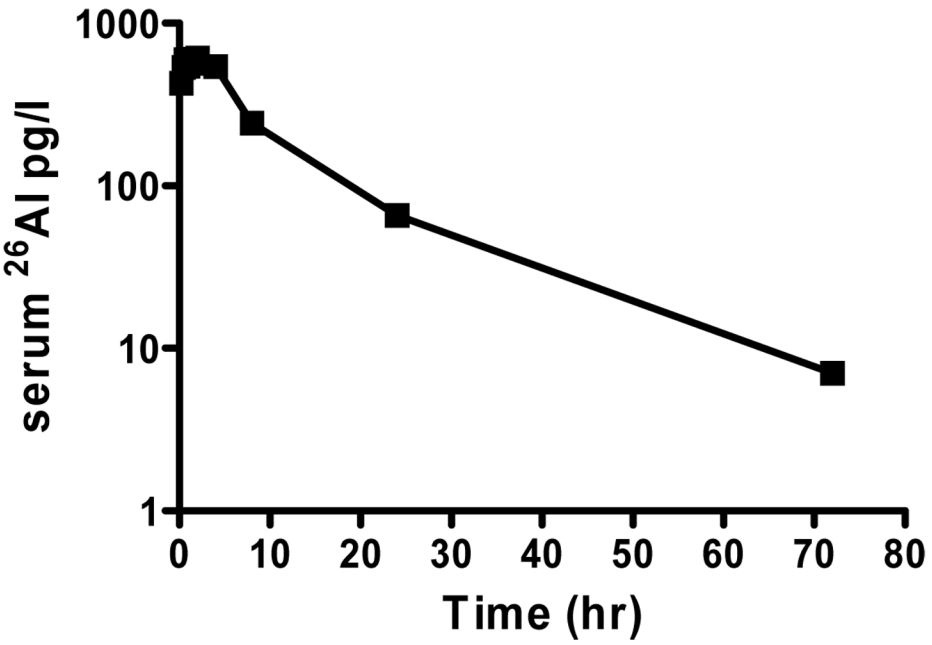

Figure 2.
Concentration of ^{26}Al in serum versus time after consumption of ^{26}Al in water. The values are mean from 5 rats at 0.25, 0.5, 0.75 h; 24 to 26 rats at 1 h; 5 rats at 1.25 and 1.5 h; 24 to 26 rats at 2, 4, 8 and 24 h and 3 rats at 72 h.

Table 1

Oral bioavailability of Al from tea infusion compared to Al in 1 or 2% acidic SALP in a biscuit, 1.5 or 3% basic SALP[a] in cheese, or in water, and absorption T_{max} and C_{max}.

	acidic SALP in biscuit[b]	1.5% SALP in cheese[c]	3 % SALP in cheese[c]	Water[d]	Tea
Oral Al bioavailability (%)	0.12 ± 0.11[e,f]	0.10 ± 0.07	0.29 ± 0.18	0.28 ± 0.16	0.37 ± 0.26 [g]
T_{max} (h)	4.8 ± 1.6	8.0 ± 2.6		1.7 ± 1.1 1.2 ± 0.9	1.25 ± 0.5 [h]
C_{max} (pg/l serum)	50 ± 33	104 ± 38		584 ± 313 659 ± 195	617 ± 244 [h]

[a] SALP = sodium aluminum phosphate

[b] Results from Yokel and Florence (2006).

[c] Results from Yokel et al. (2008).

[d] Results from Yokel et al. (2001) and Zhou et al. (2008).

[e] SALP = sodium aluminum phosphate f Values are mean ± SD.

[f] Values are mean ± SD.

[g] Significantly different from acidic SALP in biscuit results.

[h] Significantly different from acidic SALP in biscuit and basic SALP in cheese results.