



Interference of Parenteral Nutrition Components in Silicon-Mediated Protection Against Aluminum Bioaccumulation

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Abstract

Aluminum and silicon are contaminants found in formulations used to prepare parenteral nutrition. Both elements are leached from glass containers, mainly during the heating cycle for sterilization. Insoluble and biologically inactive species of hydroxyaluminosilicates have been shown to form in solutions containing Al and Si. Therefore, this interaction may play an important role in protecting the body against Al toxicity. In this study, the bioavailability of Al in the presence of Si, calcium gluconate (Gluc.), and potassium phosphate (Phosf.) was investigated in rats. The rats were divided into 10 groups of 5 animals each: control, Al, Si, Al + Si, Gluc, Gluc + Al, Gluc + Al + Si, Phosf, Phosf + Al, and Phosf + Al + Si. The doses, consisting of 0.5 mg/kg/day Al and 2 mg/kg/day Si in the presence or absence of Gluc. or Phosf., were intraperitoneally administered for 3 months. Tissues were analyzed for Al and Si content. Al accumulated in the liver, kidneys, and bones, and the simultaneous administration of Si decreased Al accumulation in these tissues. The presence of Si reduced the amount of Al present by 72% in the liver, by 45% in the kidneys, and by 16% in bone. This effect was less pronounced in the presence of parenteral nutrition compounds though. Si tissue accumulation was also observed, mainly when administered together with phosphate. These results suggest that Si may act as a protector against Al toxicity, by either reducing Al absorption or increasing its excretion, probably through hydroxyaluminosilicates formation. The presence of calcium gluconate and potassium phosphate decreases or inhibits this effect.

Keywords Silicon · Aluminum · Calcium gluconate · Potassium phosphate · Hydroxyaluminosilicates · Tissue accumulation

Introduction

Aluminum (Al) is a non-essential element with toxic properties to which humans are exposed on daily basis. Apart from gastrointestinal route, inhalation and the parenteral administration of infusions and medication are main way of Al body entrance. Upon the deposition of particles in the lungs and the delivery of infusions into the

circulatory system, Al can be distributed to all parts of the organism, facing no barriers [1, 2].

Despite the association of Al with bone and brain diseases [3, 4] in patients receiving long-term parenteral nutrition (PN) therapy [5, 6] and the accumulation of Al in the bones of premature infants receiving total PN therapy [7–9], the contamination of commercial intravenous-feeding solutions remains a problem [10–12].

In earlier studies, we demonstrated the presence of Al in injectable pharmaceutical products occurs due to their storage in glass containers [13–15]. We have also shown that not only Al but also silica can be leached from containers into pharmaceutical formulations because of the action of the solution constituents on the glass surface [16, 17]. Consequently, both Si and Al may be concomitant impurities in solutions for PN.

Due to their large volume, nutrition and infusion solutions are the drugs, administered parenterally, that have more

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adverse effects by contain contaminants [17]. Among the individual components, calcium gluconate and potassium phosphate are among the most contaminated with Al and Si [18].

Taylor et al. [19] demonstrate the high affinity of soluble oligomeric silica for aluminum at physiological pH. Traces of oligomeric silica in biological systems would profoundly affect the accumulation of aluminum. Exley et al. [20] showed hydroxyaluminosilicates (HAS) forms instantly in solutions with a considerable excess of Si, but when given more time, HAS continues to form, leading to colloid formation and subsequent precipitation, depending on the conditions. According to Guyonnet et al. [21], silica is probably the natural antidote of the aluminum and could play a benefit role by decreasing the bioavailability of aluminum. Jugdaohsingh et al. [22] showed that oligomeric soluble silica reduces Al bioavailability after intestinal resorption.

We previously investigated whether Si and Al in the amounts leached from glass containers interacted with each other to form HAS species and thus reduce Al availability [23]. In the present study, we extended this research by treating model animals with Al and Si in similar amounts to those found in PN solutions and evaluated whether Si affects Al distribution in animal tissues in the presence or absence of PN components: calcium gluconate and phosphate.

Methods and Materials

Apparatus

Measurements were carried out using an ANALYTIK Jena AG (Jena, Germany) model ZEE nit 600 atomic absorption spectrometer equipped with a transversely heated graphite atomizer, a MPE 60z auto-sampler, and a transversal Zeeman-effect background correction system. The integrated absorbance (peak area) was used to evaluate the signals. Al and Si hollow cathode lamps from Analytik Jena were employed as radiation sources. Argon 99.996% (White Martins, São Paulo, Brazil) was used as the purge gas. Atomization was performed on pyrolytic coated graphite tubes (without integrated platforms) from Analytik Jena. Temperature furnace programs and other conditions for element measurements are shown in Table 1.

For zirconium tube covering, 40 μL of a 500 mg L^{-1} Zr solution was dispensed onto the furnace, and the furnace was subjected to the temperature program described in Table 1. The procedure was repeated 25 times to obtain a deposit of 500 μg of Zr as a permanent modifier.

Table 1 Instrumental parameters for Al and Si determination by GFAAS and furnace treatment with Zr

Parameter	Al	Si	Zr treatment
Wavelength (nm)	309.3	251.6	–
Sample volume (μL)	20	20	–
Modifier (μL) ¹	Si (5)	Pd (NO_3) ₂ (5)	Zr (40)
Heating temperature program ($^{\circ}\text{C}$) (ramp time (s), hold time (s))			
Drying 1	90 (5, 20)	90 (5, 20)	90 (7, 15)
Drying 2	105 (3, 20)	105 (3, 20)	140 (10, 15)
Drying 3	110 (2, 10)	110 (2, 10)	–
Pyrolysis	1500 (250, 10)	1200 (250, 10)	1000 (100, 10)
Atomize	2600 (FP, 4)	2600 (FP, 3)	2000 (FP, 5)
Cleanout	2650 (500, 4)	2650 (500, 4)	–

¹Si: 15 mg L^{-1} ; Pd (NO_3)₂ 2 g L^{-1} ; ZrCl₂: 500 mg L^{-1}

Reagents

Aluminum chloride, sodium silicate, hydrogenphosphato, dihydrogenphosphato, and concentrated nitric acid were from Merck (Darmstadt, Germany). Calcium gluconate and tetramethylammonium hydroxide (TMHA) solution, 250 g L^{-1} , were supplied by Sigma-Aldrich (St Louis, USA). Nitric acid was further subjected sub-boiling distillation in a Berghof Teflon apparatus (Eningen, Germany). Solutions were prepared with distilled and deionized water that was further purified by a Milli-Q high-purity water device (electrical resistivity of 18.0 $\text{M}\Omega\text{ cm}$) (Millipore, Bedford, USA). To avoid Si and Al contamination from glass, only plastic materials were used. All laboratory ware (pipette tips, volumetric flasks, etc.) was immersed for at least 48 h in a 10% (v/v) HNO_3 /ethanol solution and washed with Milli-Q purified water shortly before use. To avoid contamination from the air, all sample preparation steps were conducted in a Class 100 clean bench. Standard solutions containing 50 $\mu\text{g L}^{-1}$ Al and 500 $\mu\text{g L}^{-1}$ Si were prepared by adequate dilution of a 1000 mg/L stock solution (NIST). Palladium nitrate (2.0 g L^{-1}) (Fluka, Switzerland), magnesium nitrate (1.0 g L^{-1}) (Merck), and zirconium chloride (500 mg L^{-1}) (Merck) were used as chemical modifiers for AAS measurements.

Solutions for Animal Administration

A 1.0 g L^{-1} Si solution was prepared by dissolving 0.85 g of sodium silicate (Merck) (containing 63% SiO_2 and 37% Na_2O) in 250 mL of purified water. Solutions containing 0.25 g L^{-1} Al, 1.0 g L^{-1} Si, and 1.0 g L^{-1} Si + 0.25 g L^{-1} Al were also prepared in purified water. All solutions

were prepared 2 weeks before the start of administration and used every 2 weeks. The pH of all solutions was adjusted to 7.4 with 0.1 M HCl or 0.1 M NaOH just before administration.

According to the package leaflet for injectable potassium phosphate solution 2 mEq mL⁻¹, the recommendation for an adult is 9 mmol of phosphate every 12 h. The recommended use of 18 mmol for 24 h and a 60-kg patient corresponds to 0.3 mmol kg⁻¹. For a rat weighing 200 g, the dosage will be 0.06 mmol in 0.4 mL (injection volume), corresponding to 0.15 mmol/mL. Each ampoule (1.1 mmol mL⁻¹ of phosphorus) contains 1.567 g K₂HPO₄ and 0.3 g KH₂PO₄ and water for injections q.s.p. 10 mL. To prepare the 0.15 mmol solution, 5.34 g of K₂HPO₄ and 1.02 g of KH₂PO₄ were weighed to a volume of 250 mL. The solution forms a pH 7.6 buffer, requiring no pH adjustment.

Likewise, for calcium gluconate, 1 to 2 g is recommended. Use of 1.0 g and a 60-kg patient corresponds to 0.017 g kg⁻¹. For a rat weighing 200 g, the dosage will be 0.0033 g in 0.4 mL (injection volume), corresponding to 0.0083 g mL⁻¹. 2.08 g of calcium gluconate was weighed to a volume of 250 mL. The pH of all solutions was adjusted to 7.4 with 0.1 M HCl or 0.1 M NaOH just before administration.

Al and Si in these of calcium gluconate and phosphate solutions were measured by GF-AAS for contamination determination.

An experiment was carried out to check the concentrations of Al and Si in the solutions administered to the animals. Solutions containing 250 mg L⁻¹ Al, 1000 mg L⁻¹ Si, and both together were prepared in 250-mL plastic bottles, being the pH adjusted to ca 7. From these solutions, 2.0 mL aliquots were taken on days 1, 7, 15, and 30 after preparation. Al and Si in these sets of solutions were measured by GF-AAS.

Animal Treatment

Male adult Wistar rats (60 days old, weighing 200–300 g) were used for this experiment. The animals were kept in an appropriate animal cabinet with forced air ventilation, a 12-h light/dark cycle, and a controlled room temperature of 22 °C, with ad libitum access to food (Puro Trato, RS, Brazil) and water. The animals were given intraperitoneal injections for five consecutive days followed by 2 days of no treatment each week, comprising a total of 60 administrations (12 weeks). Animals were divided into ten treatment groups: (1) control group, saline ($n=5$); (2) Al group, 0.5 mg Al/kg/day ($n=5$); (3) Si group, 2 mg Si/kg/day ($n=5$); (4) Al + Si group, Al 0.5 mg Al/kg/day plus 2 mg Si/kg/day ($n=5$); (5) Gluc group, 0.017 g Gluc. Ca/kg/day ($n=5$); (6) Gluc + Al group, 0.017 g Gluc. Ca/kg/day plus 0.5 mg Al/kg/day ($n=5$); (7) Gluc + Al + Si group ($n=5$), 0.017 g Gluc. Ca/

kg/day plus 0.5 mg Al/kg/day and 2 mg Si/kg/day; (8) Phosp group, 0.3 mmol phosphate/kg/day ($n=5$); (9) Phosp + Al group, 0.3 mmol phosphate/kg/day plus 0.5 mg Al/kg/day ($n=5$); (10) Phosp + Al + Si group, 0.3 mmol phosphate/kg/day plus 0.5 mg Al/kg/day and 2 mg Si/kg/day ($n=5$). Total volume of solution injected per day was 400 µL per 200 g of body weight. Animals were weighed weekly.

Animals were euthanized 24 h after the last treatment, and the lungs, liver, kidneys, bone (femur), testicles, muscle, brain, and heart were removed. The protocol for this study followed the guidelines of the Committee on Care and Use of Experimental Animal Resources of the Federal University of Santa Maria, Brazil. This study was approved by the Ethics Committee on the Use of Animals of Santa Maria (Protocol n° 71/2010).

Serum Samples

Blood samples were collected by cardiac puncture performed under terminal anesthesia. Serum separation was achieved by centrifugation at 2400 rpm for 15 min. Serum samples were diluted 1:1 with purified water before Al and Si determination by Graphite Furnace Atomic Absorption Spectrometry (GF-AAS).

Sample Treatment

Samples were digested following previously described a treatment [24]. Briefly, samples were weighed (0.2–0.3 g) and placed in previously decontaminated plastic flasks, and 0.5 mL of 250 g L⁻¹ TMAH was added. Flasks were kept in a water bath at 100 °C for 1 h and 24 h at room temperature (25 °C). Then, the volume was raised to 10 mL with purified water, and the Si and Al contents were determined by GF-AAS.

Bone Sample Treatment

Because bone is composed mainly of an inorganic matrix of hydroxyapatite (calcium phosphate), there was no complete dissolution of the sample with TMAH. For bone digestion, 0.5 mL of sub-boiling distilled nitric acid was used. The mixture was kept in a water bath at 90 °C for 1 h. After dissolution, the volume was made up to 10 mL [25].

Statistical Analysis

Data are expressed as the mean ± standard deviation (SD). Data comparisons were carried out by analysis of variance (two-way ANOVA) followed by Duncan's multiple range tests, where $p < 0.05$ was considered statistically significant. All analyses were performed using the GraphPad InStat software.

Results

The amount of Al and Si in the preparation administered to the animals was calculated to correspond to the contamination level of both elements found in typical commercial formulations for parenteral nutrition [19]. In this previous study, we demonstrated that the Si concentration in these products is on average four times higher than the Al concentration. Thus, in the present study, the dose was prepared to contain 0.5 mg Al kg⁻¹ and 2.0 mg Si kg⁻¹. Nevertheless, due to the possibility of Al and Si to precipitate or adhere onto the container inner surface over time, we carried out an experiment to measure Al and Si concentration in the bulk solution during a period of 1 month, at days 1, 7, 15, and 30 after solution preparation. The results showed that on day 1, Al concentrations in both solutions were diminished to 250 mg L⁻¹ in the Al solution and 270 mg L⁻¹ in the Al + Si solution. After 7 days, concentrations dropped to 230 mg L⁻¹ and 265 mg L⁻¹, respectively. After 15 days, Al concentrations in both solutions became the same, which was 250 mg L⁻¹, and remained at this level until day 30. Notably, Si concentration remained unchanged during the entire time interval. Whereas the concentrations found are very close to those expected, there was no need to correct the doses administered.

Al and Si concentration in the solutions of calcium gluconate 0.01875 mmol L⁻¹ and potassium dihydrogen phosphate 0.1835 mmol L⁻¹ was determined to verify the contamination of the salts with these elements. In the phosphate solution, the concentration of Al and Si found was 70.45 µg L⁻¹ and 4.19 µg L⁻¹, respectively, and in the gluconate solution was 42.09 µg L⁻¹ of Al and 58.76 µg L⁻¹ of Si. These values can be considered low when compared to the amounts used in the solutions administered to the animals, 0.25 g L⁻¹ of Al and 1.0 g L⁻¹ of Si.

Al Distribution in Al-Treated Organs of Rats

Aluminum was measured in seven different tissues of organs, namely, liver, kidneys, muscle, heart, lungs, testicles, and bone (Table 2). Only in three tissues of organs (bone, liver, and kidney) was Al increased in the Al group relative to the control group. The highest level was found in the liver, followed by bone and the kidneys. In all these tissues, the Al level was more than 1000 times higher than that in the control group (Fig. 1).

The results for serum and brain have already been reported in an earlier publication where the distribution of Al in different brain regions was evaluated [26]. Nevertheless, we presented the results for serum and brain here to

Table 2 Al (µg/g ± SD, n = 5) concentration in tissues of adult rats in the different treatment groups

Tissue	Treatment									
	Control	Si	Al	Al + Si	Gluc	Gluc + Al	Gluc + Al + Si	Phosf	Phosf + Al	Phosf + Al + Si
Liver	0.68 ± 0.31	0.43 ± 0.28 ^b	17.14 ± 4.29 ^a	4.71 ± 1.76 ^{ab}	0.79 ± 0.41c	42.63 ± 3.06 ^a	42.65 ± 5.54 ^a	1.70 ± 0.43 ^{ad}	6.40 ± 1.41 ^a	10.62 ± 0.99 ^{ad}
Bone	1.19 ± 0.32	0.85 ± 0.22 ^b	15.64 ± 3.55 ^a	13.25 ± 1.62 ^a	0.25 ± 0.11 ^{ac}	11.22 ± 1.64 ^a	7.18 ± 1.81 ^{ac}	0.44 ± 0.06 ^{ad}	9.78 ± 2.14 ^a	9.43 ± 1.60 ^a
Lung	1.38 ± 0.47	1.06 ± 0.49	1.31 ± 0.08	1.93 ± 0.41 ^{ab}	2.29 ± 0.44 ^c	6.40 ± 1.04 ^a	6.29 ± 0.22 ^a	3.36 ± 0.41 ^{ad}	5.49 ± 0.68 ^a	9.23 ± 0.70 ^{ad}
Kidney	0.21 ± 0.02	0.12 ± 0.08	1.87 ± 0.42 ^a	1.03 ± 0.50 ^{ab}	1.13 ± 0.14 ^{ac}	4.38 ± 0.84 ^a	3.20 ± 0.25 ^{ac}	1.81 ± 0.25 ^{ad}	1.73 ± 0.18 ^a	2.54 ± 0.11 ^{ad}
Muscle	0.20 ± 0.51	0.23 ± 0.17	0.11 ± 0.09	0.13 ± 0.09	0.32 ± 0.07 ^a	0.32 ± 0.04 ^a	0.35 ± 0.11 ^a	1.95 ± 0.49 ^a	1.54 ± 0.24 ^a	1.81 ± 0.14 ^a
Heart	0.57 ± 0.32	0.29 ± 0.32	0.30 ± 0.33	0.22 ± 0.21	1.71 ± 0.20 ^{ac}	1.18 ± 0.26 ^a	1.31 ± 0.26 ^b	1.80 ± 0.41 ^a	1.70 ± 0.26 ^a	1.95 ± 0.22 ^a
Testicle	1.26 ± 0.15	1.17 ± 0.32	1.26 ± 0.23	1.34 ± 1.41	1.56 ± 0.32 ^c	3.34 ± 0.34 ^a	2.40 ± 0.11 ^{ac}	1.00 ± 0.16 ^{ad}	3.14 ± 0.40 ^a	2.64 ± 0.44 ^{ad}
Brain	0.08 ± 0.06	0.21 ± 0.12	0.21 ± 0.14	0.27 ± 0.04 ^a	1.07 ± 0.32 ^a	1.15 ± 0.19 ^a	1.42 ± 0.22 ^a	1.05 ± 0.25 ^a	1.43 ± 0.33 ^a	1.51 ± 0.06 ^a
Serum*	1.66 ± 0.11	1.61 ± 0.15	50.52 ± 9.67 ^a	30.75 ± 6.04 ^{ab}	3.97 ± 0.32 ^{ac}	31.06 ± 1.05 ^a	28.17 ± 3.52 ^a	9.00 ± 0.71 ^{ad}	74.35 ± 5.11 ^a	85.47 ± 3.14 ^{ad}

* Conc. µg/L; ^a different from control group, ^b different from Al group, ^c different from Gluc + Al group, ^d different from Phosf + Al group. One-way ANOVA–Duncan's test ($p < 0.05$)

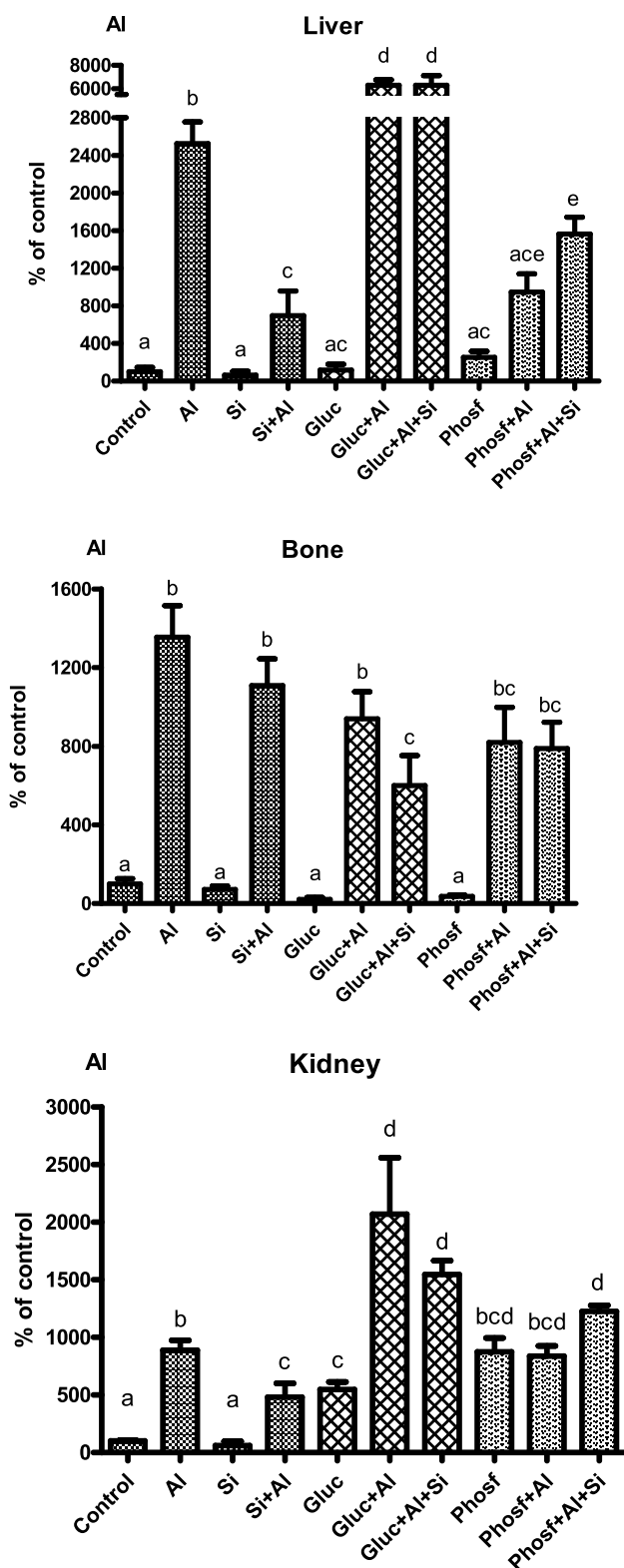


Fig. 1 Al concentration in the liver, bone, and kidneys. Different lowercase letters indicate a significant difference between groups. Bars represent means \pm S.D. ($n=5$) a control percentage. Two-way ANOVA–Duncan's test

collate the results of all tissues. Serum Al in the Al group was 30 times higher than that in the control group, and the amount of Al in the brain rose from 0.08 to 0.21 $\mu\text{g g}^{-1}$ among the same groups.

Si Distribution in Si-Treated Organs of Rats

Silicon was measured in six different tissues of organs, namely, liver, kidneys, muscle, heart, lungs, and testicles (Table 3). Si was not measured in bone, as bones did not solubilize with TMAH, and sample digestion with nitric acid, which allowed bone digestion for Al measurement, was not suitable for Si measurement. Measuring Si in an acid milieu is not feasible, and attempts to neutralize the acidity lead to the formation of precipitates (calcium phosphate). Sample centrifugation and the measurement of Si in the supernatant did not provide reproducible results.

Silicon did not accumulate in the liver, muscle, heart, and testicles, since no significant differences were observed among the animals of the Si group and the control group. On the other hand, a significant increase of Si was detected in the lungs and kidneys of the Si group. The amount of Si in these tissues was twice that found in the control group.

The concentration of Si in serum as well as in the brain increased with Si administration. The serum concentration rose from 12 to 99 $\mu\text{g L}^{-1}$, and that in the brain rose from 0.6 to 2.5 $\mu\text{g g}^{-1}$.

Al Distribution in Gluconate and Phosphate-Treated Organs of Rats

In the co-administration of gluconate or phosphate with aluminum, this same order of levels of the metal in the tissues is observed (Table 2), but with a much greater accumulation in the gluconate treatment.

The concentration of Al is different of control after gluconate administration in the bone, kidney, muscle, heart, and serum. In the liver, lungs and testicles have not difference significative compared with control group. Except in bone, where accumulation decreases, an increase in metal in these tissues is observed.

In phosphate treatment, Al concentration is high for all tissues compared with control, except for bone, where the opposite occurs.

Si Distribution in Gluconate and Phosphate-Treated Organs of Rats

A significant increase of Si was detected in the muscle, testicle, brain, and serum of the Gluc group (Table 3). There was no significantly increased in the liver, kidney, heart, and bone compared to the control animals. In phosf group, this

Table 3 Si ($\mu\text{g/g} \pm \text{SD}$, $n = 5$) concentration in tissues of adult rats in the different treatment groups

Tissue	Treatment									
	Control	Si	Al	Al + Si	Gluc	Gluc + Al	Gluc + Al + Si	Phosf	Phosf + Al	Phosf + Al + Si
Liver	8.80 ± 1.49	9.42 ± 1.43	6.92 ± 2.11	8.81 ± 1.45	11.21 ± 4.50	9.70 ± 4.06	10.64 ± 3.54	12.68 ± 3.05	15.44 ± 1.57	19.14 ± 6.76 ^a
Lung	8.80 ± 2.55	16.48 ± 1.88 ^a	10.54 ± 1.61	8.09 ± 1.59	8.07 ± 2.56	12.71 ± 1.49	10.75 ± 3.34	56.14 ± 9.32 ^a	87.21 ± 8.36 ^a	85.71 ± 6.51 ^a
Kidney	6.21 ± 0.52	14.03 ± 2.43 ^a	2.77 ± 1.68 ^b	11.16 ± 1.16 ^b	6.05 ± 0.70	6.92 ± 1.77	6.13 ± 1.59	4.88 ± 0.42	6.64 ± 0.06	4.46 ± 0.43
Muscle	1.02 ± 0.74	0.94 ± 0.47	1.04 ± 0.64	0.64 ± 0.41	2.18 ± 0.21 ^a	3.63 ± 0.22 ^a	5.65 ± 0.27 ^a	2.64 ± 0.15 ^a	2.15 ± 0.50 ^a	2.03 ± 0.33 ^a
Heart	1.42 ± 0.77	2.11 ± 0.44	1.64 ± 0.46	2.03 ± 1.20	1.74 ± 0.80	0.56 ± 0.21 ^a	1.11 ± 0.22	26.95 ± 0.92 ^a	3.38 ± 0.32 ^a	3.40 ± 1.91 ^a
Testicle	1.01 ± 0.56	1.38 ± 0.27	1.62 ± 0.45	1.30 ± 0.08	2.78 ± 0.70 ^a	1.56 ± 0.43 ^a	2.35 ± 0.59 ^a	10.19 ± 1.72 ^a	5.92 ± 0.73 ^a	10.56 ± 1.24 ^a
Brain	0.56 ± 0.34	2.53 ± 0.20 ^a	2.40 ± 0.21 ^a	2.49 ± 0.13 ^a	3.28 ± 0.59 ^a	2.36 ± 0.23 ^a	2.75 ± 0.40 ^a	2.06 ± 0.12 ^a	2.40 ± 0.21 ^a	2.47 ± 0.40 ^a
Serum*	12.21 ± 4.23	99.21 ± 6.73 ^a	24.84 ± 4.58 ^a	88.07 ± 4.89 ^a	48.39 ± 9.33 ^a	42.21 ± 4.83 ^a	56.98 ± 3.15 ^a	40.32 ± 1.60 ^a	38.44 ± 1.78 ^a	41.51 ± 2.01 ^a

* Conc. $\mu\text{g/L}$; ^adifferent from control group. One-way ANOVA–Duncan's test ($p < 0.05$)

increase not only occurs in the liver and kidney. In the lung, heart, testicle, and muscle, the amount of Si is six, nineteen, ten, and two times that found in the control group.

In serum, in both treatments, the Si concentration is close to 4 times that of the control.

Al Distribution in Al + Si-Treated Organs of Rats With or Without Gluconate or Phosphate

Compared with the control group, Al increased in the liver, bones, and kidneys in Al + Si group just as in the Al group. Similar to the Al group, no significant differences were observed in the other tissues compared with the control group. However, the amount of Al in the liver and kidneys significantly decreased compared with the Al group when Si is co-administered. These results are shown in Fig. 1. In these tissues, Al also decreased in the Si-only group compared with the control group, i.e., when administered alone, Si was able to reduce the Al distribution, even in the no Al-treated group. By contrast, the Al concentration in the lungs significantly increases when Al was administered along with Si (compared with the control, Si, and Al groups).

The presence of Si reduced the serum Al concentration by almost half. By contrast, Si promoted an increase in Al in the brain, even in non-Al treated animals, and Si was not able to reduce Al levels in the brains of Al + Si-treated animals (Table 2).

The concomitant injection of parenteral nutrition components interferes in the decrease of Al concentration observed. Only in bone in Gluc + Al + Si was observed a decrease in Al accumulation. In the liver, lung, kidney, and serum, the Al level is higher in Phosp + Al + Si compared with Phosp + Al and Phosp groups.

Si Distribution in Al + Si-Treated Organs of Rats With or Without Gluconate or Phosphate

In the liver, muscle, heart, and testicle tissues, there were no significant differences between the Al + Si group and the control, Si, and Al groups.

Already, in both tissues that presented increased Si in the Si group, the lungs and kidneys, Si was reduced in the Al + Si group, i.e., the concomitant presence of Al reduced Si deposition in these tissues (Table 3).

The remaining tissues showed no significant differences between the Al + Si group and the control, Si, and Al groups.

Serum Si was increased to the same level as in the Si group, i.e., Al did not alter serum Si levels. The same was observed in the brain; both the Si and Al + Si groups presented increased Si levels compared with the control group, and the same increased level was observed in both groups.

In phosphate treatment, the administration of Al together with Si reduces the concentration of the latter only in the heart (compared to the Phosp group). This can also be seen in gluconate treatment.

Discussion

Increase Al deposition occurred in the liver, bones, brain [26], and kidneys of the animals in the Al group. The highest concentrations were observed in the liver and in the bones. The deposition of Al in bone is well documented. Bone disease mediated by Al-induced osteotoxicity has been observed in adult and pediatric patients with preserved renal function undergoing long-term administration of total PN [27–30]. Al-loaded parenteral nutrition-associated metabolic bone disease is manifested primarily as osteopenia and fractures.

Al and Si administration resulted in a significant increase in the brain Al content. In this case, Si seems not to act as a protector, increasing metal concentration compared to the control group. These data have already been presented and commented on in our previous work [26].

Fiejka et al. [31] also found high concentrations of Al in the liver and bones after intraperitoneal administration of aluminum hydroxide to mice. The highest concentration in the liver was $265 \mu\text{g g}^{-1}$ after exposure to only 2 mg Al. Dose-dependent Al accumulation was observed in the tibia, with the highest level of Al, $23.5 \mu\text{g g}^{-1}$, observed after treatment with 6 mg. On the other hand, the Al concentration in the brain did not change significantly during Al treatment.

Alemmari et al. [32] observed liver injury in pigs, by elevated bile acids and by blunting of the bile canaliculi microvilli, who received intravenous aluminum chloride and confirmed that hepatic Al concentrations correlated with the duration of Al exposure. Massoud et al. [33] evaluate the hepatotoxic effects of different sublethal concentrations of Al_2O_3 nanoparticles using integrated bio chemical, antioxidant, and histopathological biomarkers. Several hepatic histopathological alterations were recorded ranging from adaptive responses to permanent damage. The recovery period using toxicant-free water led to an obvious reduction in the Al content in the liver, and antioxidant enzymes in addition to regressive histopathological alterations based on the frequency of alterations occurrence and the extent of affected areas.

Souza-Monteiro et al. [34] showed that AlCl_3 was capable of increasing Al circulating levels in blood. It was able to promote changes in the mineral content and triggers significant changes in the mineralized bone microstructure, such as number and thickness of trabeculae, being associated with alveolar bone loss.

In an earlier study [2], we found that the administration of Al to 2-month-old rats caused an increase in Al concentration

in all tissues, although the highest levels were also found in the liver, bones, and in the kidneys. The dose administered to the animals (24.8 mg/kg/day), however, was almost 50 times higher than those used in the present study, although over a shorter period of time (10 days). In the same earlier study, newborn rats receiving a lower dose of 0.12 mg/kg/day (closer to the dose used in the present study) showed increased Al levels only in the liver and muscle. The design of these two studies differs, since in the previous study, animals were killed 20 and 40 days after the end of the treatment. Nevertheless, the results consistently show that liver, bones, and kidneys are the main targets for Al storage.

Little is known about the distribution of Si in mammalian species, especially in humans. Jugdaohsingh et al. [35] attribute the absence of detailed studies on the physiological levels of Si in humans and other animals to the complexity of aqueous silicate chemistry and the difficulty of Si measurement.

Reffitt et al. [36] reported the pharmacokinetics and metabolism of Si in healthy volunteers after ingestion of orthosilicic acid in water. They found high clearance and renal filterability of Si and suggested that orthosilicic acid is readily absorbed by the human gastrointestinal tract and also readily excreted in urine.

In our study, the amount of Si found in the control group may count as the basal level of the element in the study model. The lowest concentration, $0.6 \mu\text{g g}^{-1}$, was found in the brain and varied from 1.0 to $2.1 \mu\text{g g}^{-1}$ in the muscle, heart, and testicles and from 6.2 to $16.5 \mu\text{g g}^{-1}$ in the liver, lung, and the kidneys.

Jugdaohsingh et al. [37] evaluated the Si concentration of connective tissues in rats of different ages. Although contemplating a different goal, they analyzed the serum, heart, lung, kidneys, and liver of 8-week-old female Sprague–Dawley rats, which yielded similar results for the heart compared with the present study ($\sim 1 \mu\text{g Si g}^{-1}$). The concentrations in the other tissues ($< 0.5 \mu\text{g Si g}^{-1}$) were lower than those found in our study, and the serum level of Si measured was much higher: whereas we measured $14 \mu\text{g L}^{-1}$ Si, they found $\sim 1500 \mu\text{g L}^{-1}$. These values differ greatly, even considering that the model animals are from different strains. As we did not measure the amount of Si in the feed and drinking water consumed by the animals as they did, these sources are unlikely to account for the differences.

Lugowski et al. [38] reviewed Si determination by focusing on patients with silicone breast implants. These authors related numerous difficulties in the determination of Si and stressed the need for standard reference materials for this element. Van Landeghem et al. [39] also reported that research in this field is complex and often prone to analytical difficulties and inaccuracies.

The influence of Si on Al bioavailability was primarily demonstrated in fish [40]. Aluminum concentrations of

6–7 μM and low pH were revealed to be lethal to Atlantic salmon. Nevertheless, fish were able to survive this acute toxic combination. No deaths occurred in the presence of 100 μM of silicic acid, gill structure remained normal, and systemic absorption of Al into the bones, brain, and other organs was inhibited.

Studies demonstrate the influence Si in preventing tissue Al retention after oral exposition [19, 41–45]. The results confirmed that Si effectively prevents gastrointestinal Al absorption and may therefore protect against the neurotoxic effects of Al. A possible relation between Al and Si levels in drinking water and the risk of Alzheimer's disease (AD) has been established. Furthermore, Si is suggested to have a protective effect in limiting oral Al absorption [42, 45].

In these studies, Al and Si were orally administered and were absorbed (or not) through the gastrointestinal tract. Parenteral administration does not follow the same route and, therefore, does not face the gastrointestinal barrier; there are no membranes to cross for absorption. Nevertheless, the results found in our study are similar to those where Al and Si were orally administered: in tissues where Al deposited, Si was able to reduce its concentration. In our study, simulating parenteral nutrition with long-term injections and similar concentrations of Al and Si found there, we found that Si acts as an inhibitor of Al accumulation in the kidney and liver (in assays without PN components).

Al is a ubiquitous metal; therefore, drinking water and food are already sources of contamination and the explanation for the presence of the metal in the control group. Likewise, accumulation would be expected in the Si-only treatment as well. However, in the liver, bones, and kidneys, Al also decreased in the Si-only group compared to the control group, because, even with contamination, the presence of Si, possibly due to the formation of HAS, reduces this deposition.

As already mentioned, dihydrogen phosphate and calcium gluconate are among the components of PN that are more contaminated by Al and Si. Gluconic acid and its derivatives have wide applications in food and pharmaceutical industry. This latter application is based on the outstanding properties of gluconic acid to chelate divalent and trivalent metal ions. The complexation of Al(III) with D-gluconate was widely studied in solutions of pH 2 to 10 and the formation of mononuclear complexes was assumed [46]. The addition of gluconate to treatments considerably increases Al accumulation in tissues. As the compound forms complexes with the metal, it may be interacting with extracellular Al and facilitating its entry into lipidic cells layers. This possible formation of the complex between gluconate and Al also explains why the protective effect of Si did not occur in these groups.

In most tissues, the deposit of Al and Si in the group treated with phosphate is greater than in the control. This is probably not due to contamination of the prepared solution,

as it is much smaller than that used in the treatment. We do not have a mechanism to explain these accumulations, but it appears that the presence of these PN components considerably increases the concentration of elements in tissues.

In the coadministration of dihydrogen phosphate with Al and Si does not show a decrease in the accumulation of Al in the tissues, with the exception of the testicle. Streckopytov and Exley [47] have investigated the formation of HAS in the presence of equimolar $\text{Si}(\text{OH})_4$ and fluoride (F^-) or phosphate HPO_4^{2-} . The latter resulted in the precipitation of aluminum hydroxyphosphate and inhibited the formation of HAS except where the concentration of Al was significantly in excess of HPO_4^{2-} where HAS_A was co-precipitated. There was no evidence of the formation of HAS which included phosphate in the structure. As the concentration of Al in the present study is lower than that of phosphate, the formation of HAS should not occur and for this reason in this environment, the Si does not decrease the accumulation of Al in most organs.

The formulation of parenteral nutrition varies according to the individual's needs, so it is difficult to carry out a study with the components simultaneously. But, with these results, we can infer that the protective effect of Si on Al toxicity is impaired in the presence of calcium gluconate and especially with potassium phosphate.

Conclusion

The simultaneous presence of Si and Al in preparations injected into Wistar rats was able to reduce Al levels in tissues where Al showed increased deposition. This event probably occurs due to the formation of HAS, which are stable and biologically inert compounds. The results allowed us to conclude that the presence of Si contaminated by Al may alleviate Al toxicity. Nonetheless, formulations for parenteral nutrition do not favor these findings.

Abbreviations PN: Parenteral nutrition; Gluc.: Calcium gluconate; Phosf.: Potassium phosphate; HAS: Hydroxyaluminosilicates; GF-AAS: Graphite furnace atomic absorption spectrometry; TMHA: Tetramethylammonium hydroxide; SD: Standard deviation; AD: Alzheimer's disease

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Data Availability Supporting materials will be made available upon request from the corresponding author.

Declarations

Ethics Approval This study was approved by the Ethics Committee on the Use of Animals of Santa Maria (Protocol n° 71/2010).

Consent to Participate All participants provided written informed consent.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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