Pharmacokinetic Study of Zeolite A, Sodium Aluminosilicate, Magnesium Silicate, and Aluminum Hydroxide in Dogs

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Zeolite A is a synthetic zeolite which may have therapeutic utility in osteoporotic individuals because of its ability to stimulate bone formation. A study of Zeolite A (30 mg/kg), sodium aluminosilicate (16 mg/kg), magnesium trisilicate (20 mg/kg), and aluminum hydroxide (675 mg) was designed in beagle dogs. The purpose of this study was to compare the oral bioavailability of silicon and aluminum from Zeolite A, sodium aluminosilicate, magnesium trisilicate, and aluminum hydroxide in dogs. Twelve female dogs received each compound as a single dose separated by one week in a randomized, 4-way, crossover design. Plasma samples were drawn at time 0 and for 24 hours after dosing. The concentrations of silicon and aluminum were determined by graphite furnace atomic absorption. The mean plasma silicon AUC values (±S.D.) were 9.5 ± 4.5, 7.7 ± 1.6, 8.8 ± 3.0, 6.1 ± 1.9 mg · hr/L and the mean plasma silicon C_{max} values (±S.D.) were 1.07 ± 1.06, 0.67 ± 0.27, 0.75 ± 0.31, 0.44 ± 0.17 mg/L for Zeolite A, sodium aluminosilicate, magnesium trisilicate, and aluminum hydroxide respectively. Although mean silicon AUC and C_{max} values were elevated when compared to baseline after administration of the silicon containing compounds, only the AUC from Zeolite A reached statistical significance ($p = 0.041$). The mean plasma silicon T_{max} values (±S.D.) were 7.9 ± 6.4, 5.8 ± 4.6, 6.9 ± 6.3 and 8.5 ± 3.4 hrs for Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide respectively. These values were not statistically different. The mean plasma aluminum AUC values for Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide (±S.D.) were 342 ± 111, 338 ± 167, 315 ± 69, 355 ± 150 μg · hr/L and the mean aluminum C_{max} values (±S.D.) were 29 ± 9, 27 ± 14, 24 ± 5 μg/L, 29 ± 11 respectively. The plasma aluminum T_{max} values (±S.D.) were 3.5 ± 4.1, 4.2 ± 4.3, 5.7 ± 7.3 and 5.0 ± 4.7 hrs for Zeolite A, sodium aluminosilicate, magnesium trisilicate, and aluminum hydroxide respectively. There was no statistically significant absorption of aluminum from the aluminum containing treatments.

KEY WORDS: Zeolite A; silicon; aluminum; bioavailability; pharmacokinetics; sodium aluminosilicate; magnesium trisilicate; aluminum hydroxide; dog.

INTRODUCTION:

In vitro studies on young bone have suggested a physiological role for silicon in the bone calcification process.[1,2] Silicon has demonstrated a significant increase in femoral bone mineral density in osteoporotic women.[3] Zeolite A is a synthetic zeolite which may have therapeutic utility in osteoporotic individuals because of its ability to stimulate bone formation. The results from previous studies suggest that the silicon is responsible for the pharmacologic activity of Zeolite A.[4] Zeolite A has also been shown to induce osteoblast proliferation in vitro[5] and demonstrated improved calcium utilization in chickens fed low calcium diets.[6]

Zeolite A also contains aluminum. Because of recent speculation about links between aluminum and Alzheimers disease, the absorption of aluminum from Zeolite A may be an important factor to consider. There are a host of dietary sources of aluminum which provide the average North America from 0–95 mg/day, with an average daily intake of 24 mg.[7] Many pharmaceutical preparations provide even higher doses of aluminum. An ideal product would provide greater absorption of silicon, while dosing aluminum equivalent to or lower than the amounts already absorbed through dietary and medicinal means.

An earlier study indicated that silicon is absorbed orally from Zeolite A in capsule, solution and suspension formulations.[8] During this study, the mean extent of absorption of silicon from the oral capsule, oral solution and oral suspension was 2.33, 3.44 and 2.73% respectively, relative to the intravenous bolus. The extent of absorption of aluminum relative to an IV reference from these same formulations was less than 0.1%. The purpose of this study is to compare the bioavailability of silicon and aluminum from Zeolite A, relative to their bioavailability from sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide which are common dietary or pharmaceutical sources of these elements.

MATERIALS AND METHODS:

Twelve female beagle dogs, 10–13 months of age at initiation of dosing, weighing from 7.3 to 11.6 kg were used in the study. The dogs were identified by ear tattoo. Zeolite A (N-0974) raw material (Ethyl, lot #07), sodium aluminosilicate (lot #SR00002922), magnesium trisilicate (lot #BD203), concentrated aluminum hydroxide gel, 675 mg/5 ml (lot #911187), and empty clear gelatin capsules (Jorgensen Laboratories, lot #35, and J-104A) were used. Encapsulated test article was prepared at the study site and assayed for content uniformity. Dosing was equimolar based upon silicon content and adjusted to each dog's body weight. The dogs were administered a 5 mL dose of the aluminum hydroxide gel suspension. The aluminum hydroxide was dispensed into capped amber containers, and stored at room temperature until use.

This study was designed at Whitby Research in Richmond, Virginia and was conducted at International Research and Development Corporation (IRDC) in Mattawan, Michigan. The dogs were individually housed in stainless steel cages and maintained in an environmentally controlled room. Water was available *ad libitum*. Diet was available for approximately 3 hours per day, and was provided at approximately 4 hours after dosing for 3 hours on the days of dosing. Each animal was dosed with 30 mg/kg Zeolite A, 16 mg/kg sodium aluminosilicate, and 20 mg/kg magnesium trisilicate (via capsule). The aluminum hydroxide was administered orally via gavage at 675 mg/animal (5 mL). A rinse of deionized water was administered orally by gavage to the dogs following administration of aluminum hydroxide to en-

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sure that all of the test article was delivered. Blood was obtained via the jugular vein at 0 hour (prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after dosing.

Assay Procedures:

The plasma samples were assayed for silicon and aluminum by graphite furnace atomic absorption at the University of North Carolina School of Medicine, Bioanalytical Laboratory.[9,10] The assay uses standards of silicon or aluminum to estimate plasma concentrations. All sample storage and preparation were carried out using polypropylene equipment to avoid silicon contamination from glass.

Pharmacokinetics:

Pharmacokinetic estimates were obtained using standard pharmacokinetic equations. Area under the curve (AUC) was calculated using the linear trapezoidal rule. The amount of silicon or aluminum delivered to each individual dog (mg/kg) was calculated by multiplying the percentage of silicon or aluminum measured in each dosage form by the corresponding total dose of the compound. Since doses of 675 mg of aluminum hydroxide were given to each dog, rather than doses on a mg/kg basis, the mg/kg dose of aluminum from aluminum hydroxide was estimated by multiplying the percentage of aluminum measured in the aluminum hydroxide gel by the corresponding total dose divided by the average weight of the dogs at the time the aluminum hydroxide dose was given. Silicon doses were equimolar, however, aluminum doses differed by more than an order of magnitude.

RESULTS AND DISCUSSION:

Of the 12 dogs receiving Zeolite A and magnesium trisilicate, none displayed emesis. Of the 12 dogs receiving sodium aluminosilicate, four displayed frothy or food like emesis. One of the 12 dogs receiving aluminum hydroxide displayed frothy emesis. Of the 12 dogs receiving Zeolite A, four developed soft stool or diarrhea, one dog receiving sodium aluminosilicate developed soft stool, four receiving magnesium trisilicate had soft stool, two receiving aluminum hydroxide developed soft stool.

Pharmacokinetics: Silicon

The mean concentration versus time plot of plasma silicon is illustrated in Figure 1. Baseline data from a previous study indicated that food intake caused an increase in plasma silicon.[8] These baseline plasma silicon concentrations have been incorporated with the mean silicon plasma concentrations for Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide. The mean baseline curve not only parallels the behavior of the other four treatments after 4 hours, but also matches the aluminum hydroxide curve almost perfectly. This confirms that aluminum hydroxide is a good control for silicon absorption and that the baseline is reproducible. The mean plot of plasma silicon in dogs (Figure 1) suggests that higher plasma silicon levels are obtained with Zeolite A in comparison to the other silicon containing compounds. Inspection of the concentration versus time plots for the individual dogs showed that three dogs had much higher maximum plasma silicon levels for the Zeolite A than any of the other dogs. In all other dogs, plasma silicon from the Zeolite A is comparable to or less than the plasma silicon resulting from the dosing of the other two silicon containing compounds. This suggests that Zeolite A may produce higher plasma silicon concentrations, but the absorption of silicon from the Zeolite A capsule is variable. This may be due to variable solubility and absorption of Zeolite A resulting from the differences in stomach pH. Although Zeolite A solubility is highly pH dependent, we can not rule out all other possible causes for the lack of consistency in the data. It is unlikely that the observed variability was due to diarrhea, since this phenomenon occurred 24 or

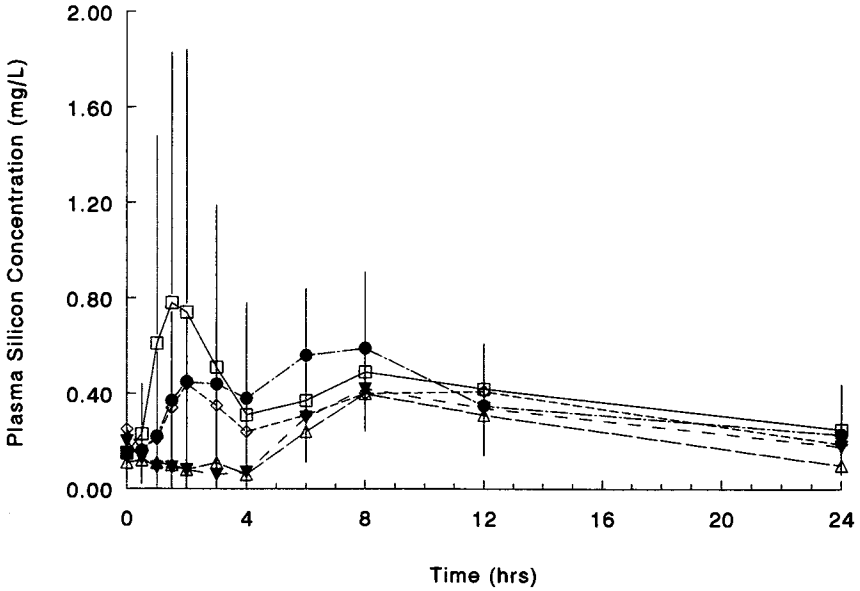

Fig. 1. Mean (±S.D.) plasma silicon concentrations from 12 dogs after oral doses of □ Zeolite A, ◇ sodium aluminosilicate, ● magnesium trisilicate, ▼ aluminum hydroxide, and △ control from previous study.

Table I. Silicon Bioavailability Estimates for 30 mg/kg Zeolite A, 16 mg/kg Sodium Aluminosilicate, 20 mg/kg Magnesium Trisilicate and 675 mg Aluminum Hydroxide

	Zeolite A		Sodium Aluminosilicate		Magnesium Trisilicate		Aluminum Hydroxide	
	Mean	std	Mean	std	Mean	std	Mean	std
Silicon dose (mg/kg)	4.66	—	4.75	—	4.63	—	0	—
C_{max} (mg/L)	1.07	1.06	0.67	0.27	0.75	0.31	0.44	0.17
$AUC_{(mg \cdot hr/L)}$	9.5	4.5	7.7	1.6	8.8	3.0	6.1	1.9
T_{max} (hr)	7.9	6.4	5.8	4.6	6.9	6.3	8.5	3.4

more hours after the dose in all cases except for one dog on day 8.

The mean silicon bioavailability parameters are found in Table I. These values have been normalized for silicon dose since they were administered on an equimolar basis according to silicon content. The mean AUC (±S.D.) for plasma silicon after dosing with Zeolite A, sodium aluminosilicate, magnesium trisilicate, and aluminum hydroxide were 9.5 ± 4.5, 7.7 ± 1.6, 8.8 ± 3.0 and 6.1 ± 1.9 mg · hr/L respectively. These AUC values were compared by a one-way ANOVA. The ANOVA indicated that there was a significant difference between the means of the silicon AUC for the four compounds ($p = 0.041$). A comparison using Tukey's standardized range test on the means only identified the value for Zeolite A as statistically greater than baseline (56% greater, $p < 0.05$).

The mean C_{max} estimates (±S.D.) for plasma silicon from Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide were 1.07 ± 1.06, 0.67 ± 0.27, 0.75 ± 0.31, and 0.44 ± 0.17 mg/L respectively. There was no statistically significant difference between the maximum concentrations ($p = 0.076$). Although not statistically significant, the mean C_{max} for Zeolite A was larger than that of any other treatment. The failure to reach statistical significance in this point estimate could be due to the variability in silicon absorption.

The mean T_{max} estimates (±S.D.) for plasma silicon from Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide were 7.9 ± 6.4, 5.8 ± 4.6, 6.9 ± 6.3 and 8.5 ± 3.4 hrs respectively. Most T_{max} values for all treatments were clustered in two groups: those with T_{max} values equal to or less than 2 hours and those with T_{max} values greater than or equal to eight hours. This suggests that early maximum concentrations may result from absorption of the silicon from the treatment, while later T_{max} values may be due to silicon absorbed from the diet. The T_{max} values were also compared using a one-way ANOVA. There was no significant difference between the T_{max} values ($p = 0.636$).

Pharmacokinetics: Aluminum

The mean plasma aluminum concentration versus time plot is presented in Figure 2. Plasma aluminum concentrations were highly variable. The peak observed at 3 hours for sodium aluminosilicate is due to an unusually high concentration observed in only one dog. This value was approximately 10-fold greater than most of the observed concentra-

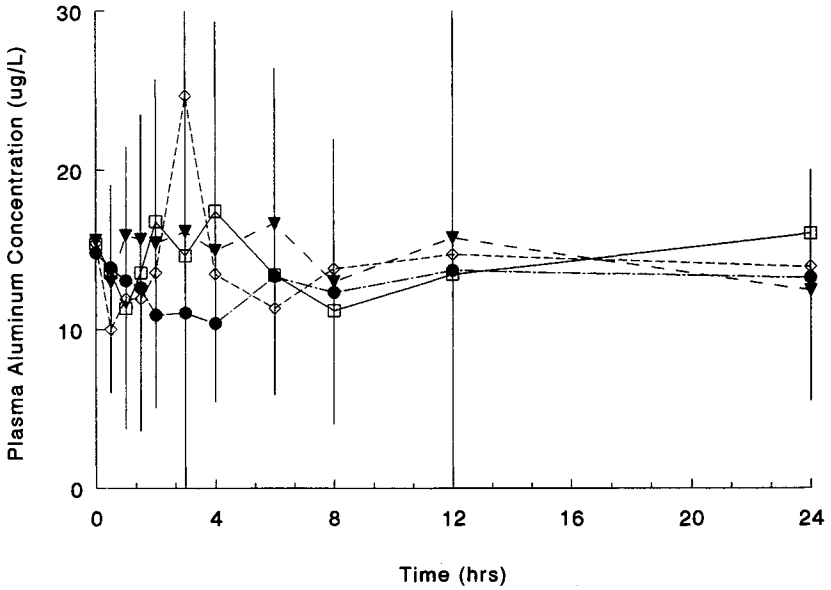

Fig. 2. Mean (±S.D.) plasma aluminum concentrations from 12 dogs after oral doses of □ Zeolite A, ◇ sodium aluminosilicate, ● magnesium trisilicate, and ▼ aluminum hydroxide.

Table II. Aluminum Bioavailability Estimates for 30 mg/kg Zeolite A, 16 mg/kg Sodium Aluminosilicate, 20 mg/kg Magnesium Trisilicate and 675 mg Aluminum Hydroxide

	Zeolite A		Sodium Aluminosilicate		Magnesium Trisilicate		Aluminum Hydroxide	
	Mean	std	Mean	std	Mean	std	Mean	std
Aluminum dose (mg/kg)	3.36	—	0.90	—	0	—	28	—
C_{max} (μg/L)	29	9	27	14	24	5	29	11
AUC (μg · hr/L)	342	111	338	167	315	69	355	150
T_{max} (hr)	3.5	4.1	4.2	4.3	5.7	7.3	5.0	4.7

* Estimated based on the average weight of dogs at time of dosing.

tions and may have resulted from analytical error. This point was omitted from calculations and estimates of pharmacokinetic parameters.

Although the silicon doses were equimolar, the corresponding aluminum doses differed by more than an order of magnitude. The amounts of aluminum delivered by Zeolite A and sodium aluminosilicate were 3.36 and 0.90 mg/kg respectively, while the aluminum hydroxide dose of 675 mg was approximately equivalent to 27.77 mg/kg aluminum based on the average weight of the dogs on the day of dosing.

In spite of the differences in the magnitude of aluminum doses, no substantial or statistically significant difference in AUC was found ($p = 0.896$). The mean plasma aluminum AUC values (±S.D.) for Zeolite A, sodium aluminosilicate, magnesium trisilicate, and aluminum hydroxide were 342 ± 111, 338 ± 167, 315 ± 69, and 355 ± 150 μg · hr/L respectively (Table II). The plasma aluminum data during magnesium trisilicate administration serves as the control treatment for the dietary absorption of aluminum as this compound contains no appreciable amount of aluminum. Although the mean plasma aluminum AUC for magnesium trisilicate was slightly lower than that of the other treatments, these data suggest that aluminum absorption from Zeolite A, sodium aluminosilicate, and aluminum hydroxide is not greater than that absorbed from dietary sources. No further dose correction of the AUC or C_{max} data were warranted as aluminum absorption was absent from the compound administered. The mean T_{max} estimates (±S.D.) for plasma aluminum from Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide were 3.5 ± 4.1, 4.2 ± 4.3, 5.7 ± 7.3, 5.0 ± 4.7 hours, respectively. There was no statistically significant difference between the T_{max} values.

Human exposure to aluminum occurs from aluminum silicates, sulfates and phosphates which are common food additives. Aluminum is also present in many natural food sources and in water supplies. The amount of aluminum ingested from natural sources and food additives in North America varies from 0–95 mg/day, with an average daily intake of 24 mg.[7] The average amount absorbed via the GI tract is 0.1% of the total intake[11] so that an estimated 0.024 mg would be absorbed daily from food.

Various analgesics and antacids deliver daily doses of 126–728 mg and 840–5000 mg of aluminum respectively.[12] A 30 mg/kg/day dose of Zeolite A to a 70 kg human would result in an aluminum dose of 235 mg/day. The amount of aluminum absorbed from pharmaceuticals may differ depending on what compounds are used and what interactions may occur with compounds ingested in the diet (such as citrates). The median fraction of aluminum absorbed from various doses of antacids in humans was estimated by Weberg et al., as 0.001–0.2%.[13] A previous study in dogs indicated that 0.03% of the aluminum dose in orally administered Zeolite A was absorbed relative to intravenous administration. Comparison of the total daily aluminum doses administered as pharmaceuticals and Zeolite A relative to their percentages absorbed, suggest that if any aluminum is absorbed from Zeolite A, it would be at the lower end of the spectrum for pharmaceuticals.

The inability of this present study to detect a statistically significant extent of aluminum absorption probably stems from the low bioavailability of aluminum and the large variability in plasma aluminum concentrations. Longer bioavailability studies may better approximate the oral absorption of aluminum from Zeolite A by taking advantage of accumulation due to the long half-life of aluminum.

In conclusion the mean silicon AUC values for Zeolite A, sodium aluminosilicate, magnesium trisilicate and aluminum hydroxide suggest that silicon is absorbed from the silicon containing products, only Zeolite A demonstrated a statistically greater absorption of silicon (56% increase) than any other treatment or baseline. The mean T_{max} values of plasma silicon suggested similar rates of absorption. The aluminum data suggest that no statistically significant absorption of aluminum occurs after the single-dose administration of Zeolite A, sodium aluminosilicate, and aluminum hydroxide.

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