Dietary Citric Acid Enhances Absorption of Aluminum in Antacids

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Ten healthy men ingested, twice daily between meals, during each of the seven-day experimental periods: (a) citric acid (as lemon juice), (b) Al(OH)₃, or (c) Al(OH)₃ + citric acid. Whole blood sampled after each dietary period was analyzed electrothermally after digestion with nitric acid. Moderate, but significant, increases in mean Al concentrations as compared with pretreatment values [5 (SD 3) μg of Al per liter] were seen after ingestion of either citric acid or Al(OH)₃: 9 (SD 4) and 12 (SD 3) μg/L, respectively. Ingestion of both Al(OH)₃ and citric acid resulted in a more pronounced, highly significant (p < 0.001) increase in Al concentrations, to 23 (SD 2) μg/L, probably owing to formation and absorption of Al–citrate complexes.

Additional Keyphrases: atomic absorption spectrometry • gastrointestinal function • diet-related effects

It is generally considered that gastrointestinal absorption of the aluminum (Al) in antacids containing Al(OH)₃ is low, and that accumulation of this element in tissues is obviated by renal elimination. However, when used as phosphate binders, these antacids may contribute to the development of encephalopathy and the osteodystrophic syndrome in patients on hemodialysis (1–3). Supporting evidence for this notion includes the growing number of case reports showing a relation between the toxic effects in the central nervous system and bone and the concentration of Al in the tissues of nondialyzed uremics given the preparations of Al(OH)₃ (4–7).

Recent animal experiments (8, 9) show that ingestion of Al–citrate complex results in substantially increased Al in blood and tissues. Complex formation between Al and dietary citrate may thus facilitate absorption or tissue retention, or both, of the drug-derived Al, and increase the risk of toxic effects.

The aim of the present study was to determine if citrate, in amounts normally present in the diet, can affect absorption of Al from drugs in humans.

Materials and Methods

Subjects. Ten healthy men (ages 23–35 years) from the Uppsala city area in Sweden volunteered to participate in the study. They were required to keep regular meal times, but no attempt was made to control the composition or Al content of their diets.

Experimental design. During the seven-day experimental periods all subjects ingested, twice daily, between meals (at about 10:00 and 20:00 hours) one of the following: (a) citric acid in the form of 200 mL of lemon juice diluted fivefold with tap water and containing 6 mg of citric acid per milliliter and <0.1 mg of Al per liter; (b) Al(OH)₃ in the form of 10 mL of an antacid suspension commonly used in Sweden ("Novalucol"; AB Hässle, Malmö, Sweden), containing 23.2 mg of Al and 17.5 mg of Mg per milliliter; or (c) both a and b taken concomitantly. Each experimental period was followed by a "balance period" (four to seven days long) during which the subjects kept normal diets.

The distribution of Al species in the presence of citric acid as a function of pH has been calculated with aid of the computer program Solgaswater (10). The equilibrium model and numeric value of the equilibrium constants developed by Öhman and Sjöberg (11) were used in the calculation procedure.

Blood was sampled on each of two consecutive weeks before the start of the experiment (control values) and at the beginning and end of each dietary supplementation period. The specimens were always collected between 07:00 and 08:00 hours, i.e., at least 12 h after the last intake of Al(OH)₃/citric acid.

Collection of specimens and analytical procedure. When blood was drawn (from a forearm vein), the first 6 mL was discarded and the next 5 mL of blood was collected (in duplicate from six of the individuals) directly into acid-precleared 5-mL plastic tubes (Labassco, Partille, Sweden). All the materials used were checked for contamination with Al: none contributed significantly to the analytical results.

The samples were transferred to quartz Erlenmeyer flasks, where they were dissolved in concentrated nitric acid that had been purified by a sub-boiling distillation in a quartz-glass chamber. All sample manipulation was performed in a class 100 environment (8). Typically, values for Al in blanks taken through the digestion procedure were about 1 μg/L. We determined Al by graphite furnace atomic absorption spectrometry, using a model AA-3030 spectrometer equipped with an HGA-500 graphite furnace, an AS-40 autosampler, and a PR-100 printer (all from Perkin-Elmer, Norwalk, CT). The analytical procedure has been described earlier (8, 12).

Results

The principal forms of Al–citrate (Cit) complexes that presumably can be formed in the acidic portion of the gastrointestinal tract are Al₄(OH)₆Cit₄, AlCit, and AlHCit (Figure 1).

Table 1 shows the Al concentrations in the blood samples. The sum of the differences in the paired values for Al from the duplicate samples (not shown) was close to zero, indicating that no random error was introduced by the analytical procedure. The atomic absorption spectrometric method we used in this study has been compared with constant-temperature graphite furnace atomic emission spectrometry (13), the favorable correlation of results showing that the analytical methodology used here is reasonably accurate.

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alone, the increase of Al concentration in blood was substantially greater in each subject when Al(OH)₃ was ingested with lemon juice—the mean for the whole group being about fivefold the control value (p <0.001). The increase was also highly significant as compared with that after lemon juice alone was ingested.

Blood Al decreased significantly during the balance period after the combined [Al(OH)₃ + lemon juice] treatment. But, just as in the two previous balance periods, it did not decrease completely to the control (pretreatment) values.

**Discussion**

The significant increase in Al in blood of healthy individuals after ingestion of Al(OH)₃-containing antacid shows that Al is absorbed from these drugs. Our findings agree with the results of earlier investigations demonstrating increased concentrations of Al in serum and in urine after the ingestion of Al-containing antacids (15–17).

The Al concentrations in blood decreased rapidly after cessation of the treatment, probably reflecting an effective renal clearance of the absorbed element in healthy individuals (1). The concentrations of Al in blood would thus appear to reflect recent exposure, rather than total body burden of Al (18, 19). However, animal experiments have shown that the increase in blood concentrations after a 10-week administration of various Al compounds was invariably accompanied by a retention of Al in brain and (or) bone tissues (9). In addition, a positive Al balance has been reported in nonurine patients, who showed a moderate increase in plasma Al after treatment with Al-containing antacids (16).

The absorption, and presumably also the tissue retention, of the Al derived from antacids is probably ordinarily too limited to induce adverse health effects. It could, however, be of clinical significance in patients with regular and high consumption of Al-containing antacids, especially in cases of renal impairment. More important, the present results clearly show that the concentrations of Al in blood can be substantially enhanced by a concomitant intake of Al(OH)₃ and Al-complex-forming dietary citrate in amounts commonly present in food or beverages. The Al complex expected to pass the gastrointestinal barrier most easily would be the nonionized Al–citrate (AlCit). Calculations in our study indicate that this Al species may have significantly contributed to the total concentration of Al compounds in the acidic environment of the stomach.
Fig. 2. Changes in Al concentration of the blood of 10 subjects at the beginning and the end of each treatment period
The vertical bars represent the medians, the boxes the upper and lower quartiles, and the horizontal bars, the maximum and minimum values (ranges) of the individual differences in Al concentrations. The positions of the boxes in relation to the zero line reflect the differences in Al concentrations in blood after the various dietary supplementations with Al; all the differences except day 0-7 (controls) are statistically significant (see Table 1)

The increased absorption of Al in the form of organic complexes might lead to a substantial accumulation of the element in tissues, especially in uremic patients, for whom Al(OH)₃ preparations are used as phosphate binders and consequently taken together with meals.

No data are available at present concerning the toxicological significance of an increase of Al body burden induced by chelation between Al and citrate. On the basis of in vitro studies, Thomas and Meyer recently suggested (20) that Al–citrate complexes are the biochemical form that inhibits the bone mineralization associated with the development of osteodystrophy in Al intoxication. However, more studies are necessary to elucidate this situation. In the meantime, dietary factors should be considered when assessing potential side effects of therapy with Al(OH)₃-containing drugs.

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References