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Intestinal absorption of aluminium in renal failure

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Abstract

The proportion of the daily ingested aluminium that is absorbed in the intestinal tract has remained a matter of debate for many years because no reliable method of measurement was available. Studies with earlier analytic techniques reported fractional absorption of aluminium from as little as 0.001% to as much as 27% of an oral dose. Measurement of ^{26}Al by high-energy accelerator mass spectrometry has permitted more accurate analyses. In normal young rats, 0.05–0.1% of ingested aluminium is absorbed in the intestine, of which roughly half goes to the skeleton within 2 h, whereas the remaining half is excreted in the urine, most of it within 48 h. Deposition in organs other than the skeleton appears to be negligible. In healthy human volunteers, the most recent estimates of fractional intestinal ^{26}Al absorption were also in the range of 0.06–0.1%. In both rats and humans, intestinal absorption of aluminium is subject to many systemic and local factors. The latter include various compounds with which aluminium is complexed in the gut lumen, and gastric acidity. The influence of food is controversial; however, absorption appears higher in the fasted than the post-prandial state. Luminal phosphate concentration decreases aluminium absorption, whereas citrate increases it. For theoretical reasons, silicates should prevent aluminium absorption, but experimental evidence has not supported this theory. Whether water hardness affects aluminium bioavailability remains a matter of debate. General conditions may also modify aluminium absorption and deposition in bone. Examples of these general factors include the uraemic syndrome, diabetes mellitus, secondary hyperparathyroidism, vitamin D status, Alzheimer's disease and Down's syndrome. Awareness of intestinal absorption of aluminium is particularly important, given that aluminium-based binders continue to be used in uraemic patients, despite the hazards of aluminium accumulation. The lessons we have learned about aluminium absorption—from the methodological difficulties of measuring it accurately to understanding the long-term clinical risks of this metal—should guide us in the safety evaluation of other potentially toxic metals that have been proposed for therapeutic use in patients with renal failure.

Keywords: absorption; accelerator mass spectrometry; aluminium; phosphate binder

Introduction

Aluminium is a major component of the Earth's crust. Each of us ingests it in small amounts every day in food and beverages. Only small amounts are found in food, resulting in a daily intake of ~4–5 mg, and the aluminium content of potable water is usually very low, between 10 and 1000 μg/l, of which <0.5% appears to be biologically available [1]. According to one calculation, the daily aluminium intake from water by humans is ~1.5 μg/kg, i.e. 90 μg for a person of 60 kg body weight, assuming a water intake of 1.5 l with a content of 60 μg/l [1]. However, with the use of aluminium-containing antacids or phosphate binders, daily doses as high as 4000 mg elemental aluminium have long been administered routinely to patients with end-stage renal disease (ESRD). Thus, these patients may have a thousand times the usual daily intake of this metal with food and water.

Normally, the digestive tract is an effective barrier against gastrointestinal aluminium absorption, and most of that which is ingested is excreted unabsorbed in the faeces. What little is absorbed is soon excreted in the urine, although some if it may also be retained in the skeleton. However, the protective function of the intestinal barrier is less effective in ESRD patients than it is in healthy individuals. This becomes clinically relevant in dialysis patients who take aluminium-based medications. Excessive aluminium is absorbed and deposited in bone and other tissues. The result is aluminium overload and intoxication, characterized by microcytic anaemia, encephalopathy and osteomalacia. Moreover, because aluminium is retained stably in the bone, even short-term ingestion of aluminium

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may lead to accumulation, incrementally adding to the total aluminium load and toxicity.

Measuring aluminium absorption

Quantifying the intestinal absorption of aluminium accurately has proved difficult. In the past, the chief problem was the unavailability of an appropriate radioisotope. The non-radioactive element ^{27}Al is ubiquitous, and because of contamination with this element and other methodological problems (unphysiologically high ^{27}Al oral loading), early studies reported extreme ranges of estimated fractional absorption—from as little as 0.001% of an ingested dose to as much as 27% [2]. At best, the early data provided rough approximations of aluminium absorption; at worst, they were totally erroneous. Another common methodological problem in attempts to quantify aluminium absorption is that changes in blood aluminium levels are a poor indicator of intestinal absorption [1]. The assessment of urinary aluminium excretion allows a better estimation in normal animals and healthy humans than estimates based on plasma aluminium kinetics, but even this type of determination does not provide any information on the amount of aluminium that has been transported to and deposited in other tissues, in particular bone.

More recently, some investigators, including ourselves, have measured the radioisotope ^{26}Al by high-energy accelerator mass spectrometry (AMS) [1,3–11]. With this technique, the lower limit of detection is 10^{-18} g, and physiological oral loads of the element can be studied [10]. Unfortunately, AMS is an extremely expensive procedure and is available at only a few facilities.

Intestinal absorption of aluminium

Intestinal uptake of aluminium is rapid in healthy young rats; however, there is considerable individual variation. Approximately 0.03% of an ingested dose appears in the skeleton within 2 h, as shown by AMS. Approximately the same amount is excreted in the urine within 48 h, with 95% of the total excretion being eliminated within this time [6,7]. Moreover, the aluminium that becomes incorporated into bone is maintained over long periods (> 30 days duration of experimental model). Accumulation in the liver and brain is much lower. Thus, while only a minute amount of the total oral load is absorbed, a clinically relevant amount of aluminium, if administered in high dose, is quickly transported to tissues that may be highly susceptible to the toxic effects of this metal.

In two human volunteers, fractional ^{26}Al aluminium absorption was estimated initially to be no more than 0.005% of the total ingested dose [10]. Subsequently, however, the same group of workers reported a much higher intestinal ^{26}Al absorption in 13 healthy subjects, namely 0.06–0.1% [5]. These estimates actually were similar to our observations in normal rats [6,7]. In human plasma, 80% or more of aluminium was found to be bound to transferrin [12].

The extent of intestinal absorption of aluminium can be affected by many local and systemic factors.

Local factors affecting aluminium absorption

The materials with which aluminium is complexed in the intestinal lumen affect the extent of its absorption. For example, cultured intestinal cells transported three times as much aluminium when the metal was linked to transferrin than when it was part of an aluminium–citrate complex, which ordinarily increases absorption (see below) [13]. Absorption of aluminium differs according to the type and amount of aluminium salt used [14]. Gastric acidity also has an effect [15], with very high and very low acidity increasing the solubility of aluminium [16]. In one study, absorption of aluminium by rats was greatly enhanced by a long fast [6]. In another study, the presence of food delayed aluminium absorption but did not modify its extent appreciably [1]. However, it is noteworthy that in the latter experiments, only blood aluminium assays were used to estimate absorption. Simultaneous phosphate ingestion decreases aluminium absorption [14], whereas citrate ingestion increases it [4,6,7,10].

How does citrate affect the kinetics and compartmentalization of oral aluminium? In normal young rats, co-administration of citrate increased absorption of a single dose of orally administered aluminium 2- to 5-fold [7]. Citrate also dramatically increased the amount of aluminium deposited in the skeleton, from 0.04% of the dose to 0.23% [7]. Moreover, even in these young animals with rapid bone turnover, the estimated residence time of aluminium in the bone was at least 500 days. Citrate also greatly increased the amount of aluminium deposited in the brain and the liver.

Theoretically, aluminium silicates could form in the gut under physiological conditions, preventing aluminium absorption. Although there is some experimental support for this hypothesis, the data are controversial. Quartley *et al.* reported that aluminium absorption can be reduced in rats by silicate administration [17]. However, an archaic analytical method of uncertain reliability was used in this study. This problem was avoided by Edwardson *et al.* in a study in healthy human volunteers. Using AMS, they likewise detected a reduction in aluminium absorption with silicate administration. However, only plasma aluminium concentrations were measured [9]. In our laboratory, there was no dose–response effect of orally administered silicon on aluminium absorption in rats, as measured in the urine, bone and brain, suggesting the absence of any effect on absorption; nor did silicon protect against citrate-mediated increases [6].

Another issue is the effect of the calcium and magnesium content in tap water on the uptake of

aluminium. In one study, water hardness (i.e. the degree of calcium and magnesium concentration in drinking water) did not affect the bioavailability of ingested aluminium [1]. However, these investigators measured only the concentration of aluminium in the blood. Thus, it is not clear how much had been transported to and deposited in bone or other tissues before or after blood sampling.

Collectively, these reports show that a number of local factors—most importantly the presence of citrate, gastric pH and fasting state—make the timing and pattern of aluminium ingestion, either in physiological amounts or after the ingestion of aluminium-based phosphate binders, a determinant in the absorption profile of this metal.

General factors affecting aluminium absorption

Likewise, a number of general factors affect aluminium absorption. The uraemic syndrome enhances intestinal uptake and tissue deposition of aluminium and other trace elements in the bone [11,18]. In rats made uraemic by five-sixths nephrectomy, serum aluminium concentrations were significantly lower than in control animals after a loading dose of the metal, but the concentration in the bone was almost twice that in control animals [11]. The difference in the fractional absorption of aluminium was not as great; the uraemic animals absorbed an estimated 0.175% of the dose *vs* 0.133% for the controls. Importantly, the serum concentration of aluminium was far lower in the uraemic animals, suggesting that ESRD both increases the absorption of aluminium and speeds its transfer to the skeleton.

Diabetes mellitus, which afflicts almost half of ESRD patients in some countries, has been suspected to enhance intestinal aluminium absorption since aluminium-related bone disease was more prevalent in diabetic than in non-diabetic dialysis patients [19]. Secondary hyperparathyroidism likewise has well-known, complex effects on intestinal aluminium transport. Thus, our group found that exogenous parathyroid hormone (PTH) administration to rats enhanced absorption, whereas secondary hyperparathyroidism associated with a low calcium diet actually led to a decrease of aluminium absorption [20]. Parathyroidectomy, however, did not appear to exert any effect [21].

Vitamin D status is another important factor in aluminium absorption. In rats with normal renal function, aluminium absorption appears to be partly vitamin D dependent [18]. Although some caution is necessary in interpreting the results, given the use of older analytical techniques, vitamin D-replete animals with normal renal function excreted twice as much of an oral aluminium dose in the urine as did vitamin D-deficient animals. The difference in excretion was far less after an intravenous aluminium dose in animals with normal renal function. These results may mean that vitamin D-replete animals absorb intestinal aluminium more efficiently. However, they could also mean that aluminium is transferred more rapidly to the bone, making it unavailable for urinary excretion. In uraemic rats, the vitamin D status had no effect on the amount of urinary aluminium excretion after oral or intravenous loads. It appears that vitamin D does not augment further the enhanced gastrointestinal aluminium absorption characteristic of uraemia.

As discussed in more detail in this issue by Cannata-Andía and Fernández-Martin, iron and aluminium share a common absorption pathway and are transported on the same serum proteins. Both in animals and in human subjects, iron overload decreases intestinal aluminium absorption, whereas iron depletion markedly increases enterocyte uptake and transcellular transport of aluminium. Similar findings were noted *in vitro* [13]. These findings suggest that susceptible individuals, such as patients with ESRD, have a higher risk of aluminium toxicity if they are iron deficient [22].

Some final examples of general conditions that affect aluminium absorption are Alzheimer's disease and Down's syndrome. Patients with Alzheimer's disease have greater than normal aluminium absorption [5]. Subjects with Down's syndrome develop neuropathology similar to the senile dementia of Alzheimer's disease. In a small series of patients, a 4- to 6-fold increase in aluminium absorption was seen in subjects with Down's syndrome compared with age-matched, healthy control subjects [8].

Conclusion

Aluminium intoxication continues to be a source of morbidity in patients with ESRD. Awareness of intestinal absorption of aluminium is particularly important, given that aluminium-based binders continue to be used in ESRD patients despite the understanding of the hazards of aluminium accumulation, aluminium-related bone disease and other complications. In animal models, 0.05% of an oral dose of aluminium appears in bone within 2 h of ingestion, indicating that the metal is rapidly absorbed and transported to the skeleton, where it can interfere with bone formation and mineralization.

Intestinal absorption of aluminium can be affected by a variety of local and general factors. Methodological problems associated with quantifying aluminium absorption have long plagued this important area of study. Today, a more precise insight into aluminium absorption can be gained using ^{26}Al AMS as the analytical method. Our understanding of aluminium absorption should serve as a cautionary tale when considering the use of other bone-seeking elements such as lanthanum for phosphate binding in patients with ESRD. Based on our experience with the limitations of analytical methods to quantify aluminium absorption accurately, we must look critically at

studies that rely solely on measures of metal blood and urinary levels, as a large portion of the absorbed metal may be transported rapidly to bone and other tissues, where it may exert sometimes dramatic effects when administered to patients over months or years.

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