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Uptake by man of aluminium in a public water supply

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1 After overnight fasting, two young male adults each received a single oral dose of 100 Bq ^{26}Al in tap water. Coincidence gamma-ray spectrometry and accelerator mass spectrometry were used to determine the ^{26}Al content of excretion collections and of blood samples.

2 Close to 100% of the intake was recovered in faeces during the first 7 days. Gastro-intestinal uptake, determined by comparing urinary excretion with patterns previously established following intravenous administration of ^{26}Al, averaged 0.22% in the two subjects.

3 Uptake fractions based on comparisons of blood concentration following ingestion and injection were much lower, but were judged to be unreliable. It is concluded that aluminium present in most water supplies is unlikely to contribute as much as 1% of a typical daily uptake of 10 μg from food.

Keywords: aluminium; bio]availability; man; water

Introduction

Interest in the biokinetic behaviour of aluminium has been stimulated by suggested associations with Alzheimer's disease,[1–3] although there is little to suggest a causal relationship.[4] It is estimated[5] that aluminium in public water supplies would only rarely add as much as 5% to the typical dietary intake of aluminium. On that basis, it would contribute only marginally to total-body aluminium, provided that no major enhancement of uptake occurred for aluminium ingested in water. Aqueous aluminium is mostly hydrolysed in neutral or weakly acidic solution; for the ingested hydroxide (the closest species for which data are available in the human) uptake of only 0.01% has been reported[6] (Table 1). However, this low availability is potentially affected by other components in public water supplies and by the specific circumstances of the intake.

Observations in rats[7] and in man (Table 1) have shown greater bioavailability following intake as citrate. Day *et al.*[8] reported a fractional uptake (f_1) from the human gastro-intestinal tract (GIT) of at least 1% under fasting conditions; for intake shortly after food, Priest *et al.*[6] found $f_1 \sim 0.5\%$. This enhanced uptake was to be expected because, in common with other organic acids and their salts, cirtrate may form complexes with aluminium and other polyvalent metal ions, holding them in solution and preventing the formation *in situ* of less soluble species such as the hydroxide. These complexes may also facilitate transport of the metal across the gut wall. By contrast, the presence of certain other substances, including silicic acid, may inhibit uptake through the local formation of insoluble complexes, such as aluminosilicates. This effect of a competitive, non-absorbed binder is well established for a number of other metals, including the alkaline-earth elements, which are bound by alginates,[9] and caesium, which is bound by Prussian Blue.[10] Citrate is largely absent from drinking water, but silicic acid is not and may be expected to affect uptake.[11]

Comparison of the results[6,8] cited in Table 1 points to recent intakes of food as a potential influence, and it is possible also that f_1 could be increased at smaller mass loads of the metal than were present in these studies. Consequently, early-morning ingestion of a very dilute solution might contribute a disproportionately large fraction of the uptake of aluminium from the diet.

The present study was designed (i) to measure the uptake under fasting conditions of aluminium in water supplied from a surface reservoir, and (ii) to assess the potential importance of water as a source of body aluminium. The approach was to derive values of f_1 from the urinary excretion of aluminium in the 5 days following intake. It thus required knowledge, available from previous studies,[12,13] of the excretion pattern following intravenous injection.

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Methods

Volunteers

The subjects (Table 2) were recruited by procedures authorized by an independent ethics committee, following its review of the study's objectives and approval of the experimental methods. They were judged to be in good health on the basis of medical history, physical examination and haematology (total leucocytes, differential leucocyte count, total red cells, haemoglobin, haematocrit, blood mean cell volume, mean cell haemoglobin, mean cell haemoglobin concentration). Normal renal function was indicated by assays of serum for urea, sodium, potassium and creatinine. Only one measured parameter was found to be outside reference limits (plasma 25-OH Vitamin D in Subject A, 12 mmol L^{-1}) and in this case the deviation from the norm was considered insignificant.

The subjects were not in receipt of any regular prescribed medication potentially affecting the uptake and metabolism of aluminium. They gave negative responses when asked about use of freely available aluminium-containing pharmaceutical preparations, about excessive alcohol consumption and about use of narcotics.

Preparation of solution for administration

^{26}Al was produced by the Joint Institute for Nuclear Research, Dubna, Russia, by the irradiation of a high-purity magnesium target with ^{4}He nuclei. Following irradiation, the ^{26}Al was chemically separated from the target. A stock solution of the isotope in a hydrochloric acid solution was prepared, with a concentration of 6.0 kBq mL^{-1}, as determined by gamma-ray spectrometry. No isotopic carrier (^{27}Al) was present.

Table 1 Bioavailability of aluminium

Compound	*Fed or fasted*	f_1*	*Reference*
Hydroxide	fed	0.01	6
Hydroxide with citrate	fed	0.14	6
As in Sydney water	fasted	0.22	This work
Citrate	fed	0.52	6
Citrate	fasted	$\geqslant 1$	8

*f_1=fractional uptake (%) from GI tract

Table 2 Details of volunteers

Subject	*Age (y)*	*Height (m)*	*Weight (kg)*	*Blood vol.* (L)*
A	22	1.83	67.6	5.0
B	31	1.72	61.8	4.5
Mean	26.5	1.78	64.7	4.7

*Blood volume estimated from weight and height[25]

Water, known to contain aluminium, was obtained from a public water supply near Sydney, Australia and transported in aluminium-free plastic containers. It was analyzed upon receipt using inductively coupled plasma atomic emission spectroscopy. The levels of Al (0.05 mg L^{-1}) and of Si (3 mg L^{-1}) were fairly typical. Other significant elements present included Ca (15 mg L^{-1}), Na (13 mg L^{-1}), Mg (6 mg L^{-1}) and S (4 mg L^{-1}).

The specified test dose for ingestion by each volunteer was 250 mL of this water (pH 6.5), containing an added 100 Bq (140.7 ng) of carrier-free ^{26}Al, i.e. a ratio (^{27}Al/^{26}Al) of 89. The labelling was achieved by addition of the appropriate volume of the stock solution. The pH of the water was re-established by the addition of dilute sodium hydroxide; it was then left to equilibrate. The concentration of ^{26}Al in the final solution was confirmed by gamma-ray spectrometry of aliquots, in a well-geometry semiconductor detector.

Radiation dosimetry

The anticipated radiation dose from ingestion of 100 Bq ^{26}Al was calculated according to a recognized dosimetry system and recommended data,[14–16] except as follows. It was assumed that the uptake fraction (f_1) was 0.01, as calculated by Day *et al*.[8] for ingestion of aluminium as citrate; although Day *et al*. had quoted this as a lower limit, it was anticipated that this would exaggerate the uptake of other bioavailable forms of aluminium, an expectation subsequently confirmed. Further, the ICRP's assumptions[14] on the behaviour of systemic aluminium were modified in line with contradictory observations[12] following intravenous injection of ^{26}Al.

The calculated Committed Effective Dose was 0.53 μSv, of which $\sim$25% was from systemic ^{26}Al, and the rest from irradiation of the GIT by unabsorbed tracer. This may be compared with the recommended limit of 500 μSv for a Category 1 volunteer study.[17]

Administration of ^{26}Al-labelled water

The intakes of 250 mL labelled water occurred at approximately 10.00 am following an overnight fast. No food was consumed until 12.30 when lunch was provided (steak, French fries, salad, cheese cake, $\frac{1}{2}$ pt lager and coffee). Records were kept by the volunteers of all food consumed in the 24 h periods preceding and following the administration.

Collection of samples

On the day before the administration, each subject provided samples for use as analytical blanks in the determination of ^{26}Al in blood, urine and faeces. In addition, a 20 mL venous blood sample was taken. This was analyzed for Ca^{+}, PO_4^{-} (inorganic), Mg^{2+}, 25-OH Vitamin D and 1,25-OH Vitamin D.

At 1, 4 and 24 h after intake, further 10 mL samples of blood were removed into heparinized vials. To exclude contamination of specimens, no blood samples were handled by persons possibly contaminated with ^{26}Al, and the sealed samples were held in areas remote from those used to prepare the injection solutions or to process excretion collections.

Volunteers collected their daily outputs of urine and faeces for 7 days after administration. 10 mL of conc. nitric acid was added to each 24 h sample as a preservative.

Analysis of faecal samples for ^{26}Al

Faecal samples were weighed, dried and heated at 500°C in a muffle furnace to a near-white ash. Each sample of ash was weighed and transferred quantitatively to a 4″ diameter plastic Petri dish, which was capped and sealed. The sample was positioned between the faces of two co-axially located, 152 mm-diameter scintillation counters within a room shielded on all sides by 100 mm of lead; the content of ^{26}Al was determined from the recorded 511 keV coincident annihilation quanta. Standards for energy and efficiency calibration were counted at least once daily.

Analysis of urine and blood samples for ^{26}Al

^{26}Al was determined by accelerator mass spectrometry (AMS) at the Australian National University, essentially as described elsewhere.[18] Each 24 h urine sample was weighed, account being taken of the added nitric acid. The collections were then combined to give bulked samples representing, for each subject, the output during 0–24 h, 24–96 h and 96–168 h. Aluminium-27 (100 mg per 24 h sample duration) was added as a yield tracer. A 1-L aliquot was removed for analysis from each bulked sample, except in the single instance of a smaller total volume, when the entire collection was processed. The aliquot for analysis was treated with sodium phosphate and neutralized to precipitate aluminium calcium phosphate. The precipitate was taken up in nitric acid, the solution was filtered and the filtrate was evapor-ated to dryness. The residue was progressively heated in oxygen to 400°C, then to 600°C and finally to 800°C to ensure complete oxidation of the aluminium. About 5 mg of the oxide was mixed with an equal mass of silver powder and packed into the sample cavity of an ion source assembly. The prepared ion sources were then used in AMS to determine the ratio ^{26}Al:^{27}Al in each. The ^{26}Al content of each urine sample could then be determined.

The heparinized blood samples were wet ashed with fuming nitric acid to zero carbon content, after the addition of 1 mg of stable ^{27}Al tracer. Iron was removed as $FeCl_3$ into di-isopropyl ether, calcium (1 mg) was added and aluminium was precipitated as the phosphate at pH 7.0. The resulting aluminium-calcium phosphate was used to prepare an ion source for AMS, in the manner adopted for urine samples. Recovery was greater than 80%.

Results

Faecal excretion

Table 3 shows the activities of ^{26}Al found in faecal voidings. The total ^{26}Al recovery over 7 days (mean in the two subjects 99 Bq, c.f. 100 Bq ingested) validates the measurement techniques, in view of the small fractions which will be shown to have been absorbed.

Minor differences are seen in the patterns of elimination of ^{26}Al by the two volunteers. Subject B had lost 66% of the dose by 27 h after administration, compared with A's loss of only 17% by 31 h; however by 47 h both subjects had excreted 94%. Table 3 includes the cumulative gastro-intestinal occupancies (time integrals of ^{26}Al activity in the GIT, expressed as Bq.d). These patterns differ only marginally, compared with the inter-subject variations recorded in a previous study of aluminium uptake by other volunteers;[6] nevertheless the higher occupancy in Subject A might be expected to promote a higher uptake by this subject.

Retention in blood

Measured concentrations of ^{26}Al in blood are given in Table 4. It includes positive values for

Table 3 Faecal excretion

Time (d)	*Fresh weight (g)*	*^{26}Al (Bq)*	*^{26}Al occupancy (Bq d)*
Subject A			
Pre-intake	242	0.13 ± 0.005[a]	–
1.29	96	16.99 ± 0.16	22
1.89	171	77.06 ± 0.70	168
2.89	207	2.97 ± 0.05	176
3.55	104	0.26 ± 0.02	177
4.93	286	0.26 ± 0.01	179
6.06	265	0.07 ± 0.02	179
Total[b]	1129	97.6	
Subject B			
Pre-intake	126	0.004 ± 0.003[a]	–
1.13	118	65.55 ± 0.63	75
1.94	125	28.19 ± 0.29	129
2.39	111	4.77 ± 0.06	141
3.32	96	1.07 ± 0.03	144
4.02	82	0.17 ± 0.01	145
4.34	108	0.20 ± 0.02	146
6.00	134	0.34 ± 0.02	148
6.49	128	0.10 ± 0.01	149
Total[b]	902	100.4	

[a]These values represent background values which were subtracted before tabulation of the ^{26}Al activities post-intake. [b]For samples post administration

the two pre-administration samples, but also similar results that had been obtained when blood from two control subjects was processed and analysed in the same way. Consequently they may be taken to represent an instrumental background response. The levels recorded after intake of the test solutions were at least a factor of four greater, and in most cases the increment was much larger.

Table 4 shows that similar concentrations of ^{26}Al in blood were detected in both subjects at 1 h after intake, by which time most unabsorbed aluminium would have been present in the stomach or upper small intestine. For Subject B, the value at 1 h was the maximum recorded in him, and the later decline during 4–24 h occurred at a rate similar to that in subjects who had received ^{26}Al by intravenous injection;[13] the inference is that uptake in this subject was substantially complete by 4 h. In contrast, the greater maximum level observed in Subject A was delayed, to 4 h, and the subsequent reduction was much less marked than in B. The explanation may lie either in a longer retention time of ^{26}Al in A's blood and/or in a more protracted and efficient uptake by this subject associated with his increased GIT occupancy (Table 3).

Table 4 Concentrations of ^{26}Al in blood and derived uptake factors

Hours after intake	*Subject*	*$^{26}Al^b$ (pg L^{-1})*	*Percent uptake^c (f_1)*
(previous day)[a]	A	0.21 (0.36)	
	B	0.35 (0.45)	
	Mean	0.28 (0.40)	
1	A	7.54	0.027
	B	8.25	0.026
	Mean	7.90	0.027
4	A	13.3	0.047
	B	6.40	0.020
	Mean	9.85	0.034
24	A	5.84	0.021
	B	1.20	0.004
	Mean	3.52	0.012

[a]Values with control blood in parentheses; statistical uncertainty (1σ) at these background levels is ±0.15 pg. [b]Pre-administration values have been subtracted from the concentrations recorded post-intake. [c]From entries in previous column, assumed blood volume (Table 2) and known intake of 140.7 ng

Urinary excretion

In Table 5 the temporal pattern of urinary excretion is derived from the quantity of ^{27}Al added to the entire sample and the isotopic ratio measured in an aliquot. In both subjects excretion of ^{26}Al was greatest during the first day, declining rapidly thereafter. In Subject A this reduction was marginally less severe, and the total excretion somewhat greater; these observations are consistent with the evidence given above for prolonged uptake in this subject.

Fractional uptake

In Table 6, uptake fractions (f_1) for ^{26}Al have been derived from the urinary excretion (Table 5). From Table 5, we estimate by interpolation that about 0.19% of the intake (A) and 0.13% (B) were lost in the first 5 days. In the six subjects of Talbot *et al*.[13] an average 72±7 (s.d.)% was recovered in urine voided in the same period after intravenous injection of ^{26}Al. On this basis, the mean uptake in A and B is 0.22%. Much lower values are presented in Table 4, calculated by a method similar to that adopted by Edwardson *et al*.[11] and by Day *et al*.[19]: the concentrations found in blood at 1, 4 and 24 h after ingestion were scaled according to each subject's estimated blood volume, and the results were expressed as fractions of the ingested quantity. Difficulties with this approach will be discussed below.

Table 5 Urinary excretion of ^{26}Al

Time	*Mass of urine excreted (g)*	*^{27}Al added to whole sample (g)*	*Ratio ^{26}Al:^{27}Al in aliquot*	*^{26}Al excreted (pg)*	*Fraction of dose excreted (%)*
Subject A					
Pre-intake	933	0.1	2.8×10^{-13}	0.028	
0–24 h	1902	0.1	1.74×10^{-9}	174	0.124
24–96 h	10456	0.3	2.70×10^{-10}	81	0.058
96–168 h	13681	0.3	8.50×10^{-11}	25	0.018
Total to 7 days				280	0.200
Subject B					
Pre-intake	2135	0.1	2.8×10^{-13}	0.028	
0–24 h	2711	0.1	1.22×10^{-9}	122	0.087
24–96 h	6882	0.3	1.86×10^{-10}	56	0.040
96–168 h	10090	0.3	4.90×10^{-11}	15	0.011
Total to 7 days				193	0.138

Table 6 ^{26}Al uptake calculated from urinary excretion

Subject	*Percentage of dose excreted to 5 days*[b]	*Percentage uptake*[a] *(f_1)*
A	0.19	0.26
B	0.13	0.18
Mean	0.16	0.22

[a]Based on assumed 72% excretion of absorbed ^{26}Al in urine[13].
[b]Estimated from data of Table 5

Discussion

Reliability of method

The validity of this study depends on the body's presumed inability to differentiate between stable and radioactive isotopes of an element in the processes of uptake and subsequent metabolism. For elements with atomic number as high as that of aluminium, there can be no such differentiation provided that the isotopes are identically speciated. The labelling procedures adopted in the present study would be expected to achieve such identity.

Table 4 demonstrates the pitfalls in attempts to assess the bioavailability of aluminium solely from isolated blood sampling. The uptake of certain elements, e.g. lead,[20] is followed by a period of essentially stable concentrations in blood, from which the absorption may be derived through comparison with the level following intravenous administration. This approach fails with aluminium, because the rapid losses[12] to other pools make the temporal pattern of blood levels too dependent on that of uptake. In this situation calculations based on the time-integrated blood concentration, determined over several days, would be more reliable, but the determination of this integral would require an impractical sampling regime. The measurement of urinary excretion over several days after ingestion offers a satisfactory alternative (Table 6). An objection might be that the renal clearance rate of aluminium declines materially with time following intravenous injection,[12,13] reflecting a changing speciation which may evolve at different rates in different subjects and affecting the relationship between uptake and excretion; nevertheless, the 0–5 days excretion in the six subjects of Talbot *et al*.[13] was reasonably consistent at 72±7 (s.d.)% of the injection.

Calculated uptake fractions

In Table 1, the mean value (0.22%) for uptake of aluminium present in Sydney drinking water is seen to fall within the range of estimates for the element otherwise presented. In practice, it is likely that acceptance of this mean would exaggerate the importance of water as a source of body aluminium, because most water is not consumed under fasting conditions, which encourage uptake, and because culinary practices introducing silicon and other elements can reduce bioavailability.

While the results provide no evidence of unexpectedly high bioavailability of aluminium in water, they do indicate an uptake of a hydrated aluminium ion in excess of that (0.01%) applying to an aluminium hydroxide suspension.[6]

Contribution to total dietary intake of aluminium

On the following assumptions:

- that a typical daily consumption of water is 1.5 L;
- that a typical level[21] of aluminium in drinking water is 20 μg L^{-1};
- that non-occupationally exposed subjects typically excrete $\sim$10 μg day^{-1} of aluminium in urine (e.g. Kaehny *et al*.[22]);
- that our value of f_1=0.22% is typical;
- that the fraction of aluminium uptake excreted is 95% (based on 5% retention of injected ^{26}Al after 1 year[12]);

the contribution to total body aluminium uptake from consumption of water may be estimated as follows:

$$\begin{aligned}
\text{Intake of Al} &= \text{volume consumed} \times \text{concentration} \\
&= 1.5 \times 20 \text{ or } \mathbf{30}\ \mu\mathbf{g\ day^{-1}} \\
\text{Uptake of Al} &= f_1 \times \text{daily intake} \\
&= 30 \times 0.0022 = \mathbf{0.066}\ \mu\mathbf{g\ day^{-1}} \\
\text{Mass excreted} &= \text{uptake} \times \text{fraction excreted} \\
&= 0.066 \times 0.95 = \mathbf{0.06}\ \mu\mathbf{g\ day^{-1}}
\end{aligned}$$

$$\%\ \text{contribution} = 100 \times \frac{\text{estimated excretion of water-derived Al}}{\text{total excretion of Al}} = \frac{100 \times 0.06}{10} \text{ or } \mathbf{0.6\%}$$

An alternative argument is as follows. Priest *et al*.[12] followed the whole-body retention of ^{26}Al in a healthy subject for more than 3 years after intravenous administration; their subject was subsequently shown to be typical in his early metabolism of injected aluminium.[13] By extrapolation of the trend established over the period of study, they concluded, with reservations, that continuous exposure over 55 years of adult life would result in an accumulated burden of aluminium in the range 160–440 times the daily systemic uptake.[12] With the estimate of 0.06 μg derived above for the component from water supplies, this would imply an accumulated deposit in the range 10–30 μg. By comparison, estimates of the deposit from all sources of aluminium are in the range 2 mg[12] to 40 mg.[23]

On the basis of either argument we may conclude that, if our subjects were typical in their metabolism of aluminium, the presence of the metal in most water supplies contributes little to the total systemic deposit; this accords with qualitative conclusions reached by Gardner and Gunn,[24] from a study conducted without the benefit of an isotopic tracer. Levels much higher than the UK median of 20 $\mu g\ L^{-1}$ are found in certain supplies elsewhere, e.g. 2.7 $mg\ L^{-1}$ in one report[5] from the United States. Even with such high concentrations, however, the mass absorbed would be no more than comparable with that from dietary intake.

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