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The bioavailability of ^{26}Al-labelled aluminium citrate and aluminium hydroxide in volunteers

N.D. Priest, R.J. Talbot, J.G. Austin, J.P. Day,* S.J. King,* K. Fifield† & R.G. Cresswell†

*Biomedical Research, AEA Technology, Harwell, Oxfordshire UK, *Department of Chemistry, University of Manchester, Manchester UK and †Department of Nuclear Physics, Australian National University, Canberra, Australia*

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A study was undertaken to determine the fraction of ingested aluminium taken up by two male volunteers, following their ingestion of either aluminium citrate or aluminium hydroxide. In addition, the effects of simultaneous citrate ingestion on the gastrointestinal absorption of aluminium from its hydroxide was studied. Volunteers received three oral doses of ^{26}Al-labelled aluminium compound in water. The doses were administered directly into the stomach using a paediatric feeding tube. Blood samples were collected from the volunteers at 1, 4 and 24 h after administration, and their daily output of urine and faeces was collected for 6 days. These samples were analysed for their ^{26}Al content using either coincidence gamma-counting or accelerator mass spectrometry. The uptake of aluminium was greatest following its administration in the citrate form and was least following intake as the aluminium hydroxide suspension. The co-administration of citrate, with the aluminium hydroxide suspension, was found to enhance the levels of ^{26}Al uptake in both volunteers. Using a urinary excretion factor based on the results of previous studies, the fractional aluminium uptake from each of the species was calculated: aluminium citrate, 5.23×10^{-3}; aluminium hydroxide, 1.04×10^{-4}; aluminium hydroxide with citrate, 1.36×10^{-3}.

Keywords: aluminium citrate, aluminium hydroxide, bioavailability, ingestion

Introduction

When present at high levels in the body, aluminium causes neurological damage, bone disease and microcytic anaemia (DeBroe & van de Vyver 1985, van de Vyver & Visser 1990, Doll 1993). To what extent these effects are produced at lower body burdens is unknown. To date, most high body burdens of aluminium have been found in patients with renal disease, which suppresses aluminium excretion. These patients received aluminium either as a consequence of the use of domestic water supplies for renal dialysis or by the gastrointestinal tract absorption of aluminium from phosphate binders.

An accurate assessment of the bioavailability of ingested aluminium is exceedingly difficult unless an isotopic tracer technique is used. This is for two main reasons: firstly, the bioavailability of ingested polyvalent metal ions is low and, secondly, studies using stable aluminium are plagued by problems of distinguishing endogenous aluminium from administered aluminium and from aluminium contamination of samples (Priest 1993). In addition, the amount, as a fraction of uptake, and temporal pattern of aluminium excretion following administration is unknown, requiring extensive assumptions to be made in order to assess bioavailability (Wilhelm *et al.* 1990). Nevertheless, several papers have been published describing aluminium bioavailability in man (Greger & Baier 1983, Weberg & Berstad 1986, Haram *et al.* 1987). These describe rather low levels of aluminium uptake. More recently, the rare isotope ^{26}Al, in combination with the analytical technique accelerator mass spectrometry (AMS), has been used to investigate the uptake of ingested isotope. These have shown that as much as 1% of the isotope administered to human volunteers may be taken up by the body under some circumstances (Day *et al.* 1991, 1994, Edwardson *et al.* 1993). However, the authors of these studies make no claims to have accurately determined bioavailability, a consequence of their reliance upon the measurement of blood aluminium levels at a single fixed time after administration, and the uncertain relationship between total uptake and levels in the blood at the time of

Address for correspondence: N.D. Priest, UPRC, Middlesex University, Bounds Green Road, London N11 2NQ, UK. Tel: (+44) 181 362 5229; Fax: (+44) 181 361 1726.

measurement. They have, however, demonstrated the utility of ^{26}Al for studies in man and of AMS for determining the isotope in biological samples.

The best assessments of bioavailability are made using dual isotope methods, where one isotope is injected into the bloodstream and another is given, at the same time, by the test route of administration—normally by ingestion. In these cases, the bioavailability is determined from the ratio of the integrated blood levels/excretion levels following intake/uptake of both isotopes. With only one isotope available for aluminium, simultaneous, dual isotope studies are not possible. It follows that an alternative strategy has to be adopted where the biokinetics of the injected aluminium is determined first and the test solutions are administered later. This strategy has been employed by the authors. First the fate of injected aluminium (and gallium) was determined (Priest *et al.* 1995a, Talbot *et al.* 1995). It was found that 72±3% (mean±SEM) of blood aluminium is excreted in the urine during 5 days following administration—most (59±4%) within the first 24 h. Subsequently, studies have been undertaken where aluminium compounds, labelled with ^{26}Al, were introduced into the stomach and the level of aluminium uptake was determined by measuring the quantity of excreted label during 6 days following the administration and then applying a correction factor of 0.72 to account for retained isotope (Priest 1994, Priest *et al.* 1995b). This paper describes one of these studies, undertaken using labelled aluminium citrate (an organically complexed form which is likely to have a relatively high bioavailability) which may be present in citrus drinks, e.g. orange juice, and labelled aluminium hydroxide which is a common component of 'over the counter' and prescribed antacids (aluminium hydroxide is relatively insoluble and was predicted to be of low bioavailability). In addition, the study examined the effect of citrate co-administration on the bioavailability of aluminium ingested as hydroxide. The latter is important because some medical procedures employ the simultaneous administration of aluminium hydroxide and citrate and some antacids may include citrate in the formulation (e.g. Maalox, Extra Strength Lemon Creme®, Rhone-Poulenc Rorer Pharmaceuticals Inc.). It may be expected that the citrate will mobilize further aluminium, leading to a higher uptake (Partridge *et al.* 1992). In addition, the experiment was designed to provide an estimate of the retention time of aluminium in the gastrointestinal tract and a measurement of the temporal pattern of aluminium excretion following its ingestion. The studies were undertaken in normally-fed, young adult male volunteers.

Methods

Volunteers

The two subjects used for the study were aged 33 (volunteer A) and 29 (volunteer B) at the time of aluminium administration and had estimated blood volumes of 5.4 and 5.1 l, respectively. They were healthy males free from cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, haematological and psychiatric disease as determined by history, physical examination and laboratory screens. Neither of the subjects had any recent history of prescribed medicine or was currently using any other pharmaceutical product.

Preparation of test materials

Test solutions/suspensions containing ^{26}Al-labelled aluminium hydroxide and ^{26}Al-labelled aluminium, trisodium citrate complex were prepared. In each case the mass of stable carrier aluminium present with the radionuclide was 100 mg. The material was administered either in the form of a 100 ml aqueous solution (in the case of aluminium citrate) or as a colloidal suspension of aluminium hydroxide. The materials were prepared as follows.

^{26}Al-labelled aluminium, trisodium citrate complex. Each 100 ml dose of citrate was dispensed from a stock solution prepared by the addition of 3.572 g of the soluble salt $AlCl_3 \cdot 6H_2O$ (analytical grade) to 400 ml of analytical grade water (equivalent to 100 mg Al^{3+} 100 ml^{-1}). To this was added 400 Bq of ^{26}Al from the stock solution of radionuclide and 4.0 g of analytical grade trisodium citrate, to give the final solution of pH 6.5.

^{26}Al-labelled aluminium hydroxide. Each 100 ml dose of aluminium hydroxide was dispensed from a stock suspension prepared by the addition of 3.572 g of the soluble salt $AlCl_3 \cdot 6H_2O$ (analytical grade) to 400 ml of analytical grade water (equivalent to 100 mg Al^{3+} 100 ml^{-1}). To this was added 400 Bq of ^{26}Al from the stock radionuclide solution, with stirring to ensure dispersion. Subsequently, 0.1 M sodium hydroxide was added drop-wise until aluminium hydroxide was precipitated as a colloid. The pH of the final suspension was then adjusted to pH 7.0.

All solutions/suspensions were prepared on the day of administration and their ^{26}Al content was confirmed by gamma-spectrometry.

Administration

For each volunteer the experiment spanned 7 weeks. On day 0 (the day prior to administration of the first preparation), samples were collected to establish base-line levels for ^{26}Al measurements in blood and excreta. The three preparations were given as follows:

day 1 ^{26}Al-labelled hydroxide.
day 21 ^{26}Al-labelled hydroxide, immediately followed by 100 ml stable citrate solution (1% trisodium citrate, pH 6.5).
day 49 ^{26}Al-labelled citrate solution.

Each dose was given at approximately 10.00 a.m. following a standardized light breakfast. No further food was consumed for a further 2–3 h. On each occasion the test aluminium was administered via a paediatric feeding tube inserted into the stomach through a nostril. The solutions were introduced into the tubes from a syringe. On completion

of this procedure all syringes and tubes were retained and investigated by gamma-ray spectrometry—no detectable residues were found.

The quantity of ^{26}Al given to each volunteer was determined by gamma-ray spectrometry, in a well-geometry semiconductor detector, of aliquots of the stock solutions prepared for administration. The estimated activities and masses of the 100 ml volumes administered were:

^{26}Al-labelled aluminium hydroxide	117 ± 1 Bq (1.65×10^{-7} g)
^{26}Al-labelled aluminium, trisodium citrate	112 ± 1 Bq (1.58×10^{-7} g)

Radiation dosimetry and ethics

The likely radiation doses to be received by each volunteer were calculated prior to the study in order to demonstrate conformity with World Health Organization guidelines for human volunteer studies conducted with ionizing radiation. The doses were calculated for an administration of 100 Bq ^{26}Al at each dose. For the calculation it was assumed that the absorbed fraction (f_1) was 0.01 for each compound, in accord with the value calculated by Day *et al.* (1991) following a citrate study conducted at Manchester. This value was assumed to be, and was subsequently shown to be, conservative. The radiation doses for tissues and organs, other than the gut compartments, were scaled from those calculated following a previous study in which 0.5 kBq ^{26}Al was injected into a volunteer. The doses to the gut compartments arising from the passage of non-absorbed aluminium were calculated using the ICRP 30 dosimetry system (ICRP, 1981) and data, but using tissue weighting factors recommended in ICRP 60 (ICRP, 1991).

The doses calculated were 0.53 μSv for each administration. Of this dose only about 25% was attributable to absorbed ^{26}Al. It follows that the calculated total dose for each volunteer receiving three solution administrations was 1.6 μSv. This dose is about 320 times lower than the World Health Organization dose limit of 500 μSv for a Category 1 volunteer study (WHO, 1972) and about 0.05% of the dose received by the volunteers from background radiation each year. Details of the dosimetric calculations are described elsewhere (Priest 1994).

The study was approved by the AEA Technology Ethics Committee (TISAC) and was conducted following the receipt of a UK Department of Health ARSAC (Administration of Radioactive Substances Advisory Committee) Certificate and the informed consent of the volunteers.

Samples collected

At 1 day prior to administration and at $1\,h \pm 10$ min, $4\,h \pm 30$ min and $24\,h \pm 1\,h$ after each dosing 10 ml samples of blood were removed, from the median cephalic vein, for ^{26}Al determination by AMS. To exclude contamination of specimens, no blood samples were handled by persons possibly contaminated with the radioisotope and the sealed samples were held in a laboratory remote from those used to prepare the injection solutions. In addition, volunteers collected their total daily output of urine and faeces for 6 days following each dosing procedure. For individual faecal samples, the volunteers recorded the time of voiding. For daily urine samples, the volunteers noted the time of each addition to the bulked 24 h sample. Each urine collection bottle had 10 ml of concentrated nitric acid added to act as a preservative. No lost or missed samples were reported.

Analysis

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

Each 24 h urine sample was weighed, account being taken of the mass of the screw-cap bottle and the added nitric acid. The samples were then further acidified and evaporated to dryness under IR lamps. The residues were transferred to the Department of Chemistry, University of Manchester for the preparation of ion sources for AMS analysis. The ion source preparation required the dissolution in nitric acid of the dried residue followed by the immediate addition of a known quantity of stable ^{27}Al yield tracer (3–5 mg). The aluminium-containing solution was then divided into duplicate aliquots and analysis proceeded on one—the remainder being retained for confirmatory analysis if required. The aliquot for analysis was treated to remove aluminium from the solution by the addition of calcium followed by phosphate precipitation at pH 7.0. The dissolved precipitate was then stripped of both calcium and iron by solvent extraction. Ion sources were prepared by the evaporation of the aluminium nitrate solution dispensed into the sample cavity of the ion source. These were then subsequently fired at 900°C in oxygen to produce aluminium oxide.

The prepared ion sources were despatched by courier to the Department of Nuclear Physics, Australian National University, Canberra, Australia, where they were analysed to determine the ratio of ^{26}Al:^{27}Al in each source by AMS using the Canberra Van de Graaff accelerator. The ^{26}Al content of each urine sample could then be determined.

Blood samples, after the addition of anti-coagulant, were transferred to the University of Manchester without further treatment. These were wet ashed with fuming nitric acid to zero carbon content after the addition of 1 mg of stable aluminium tracer. Iron was removed as $FeCl_3$ into di-isopropyl ether, calcium was added (1 mg) and aluminium precipitated as the phosphate at pH 7.0. Aluminium/calcium phosphate transferred to ion source was then baked at 900°C in oxygen for 6 h to produce oxide. Product recovery was greater than 80%. Analysis was by AMS.

Results

Gut retention and faecal excretion

The gut retention and faecal excretion of the administered ^{26}Al for both volunteers are shown in Table 1 and in Figure 1. Both volunteers produced regular faecal samples, with volunteer A averaging 0.94 voidings per day and volunteer B averaging 1.2 voidings per day. The mass of faeces voided on each occasion was very variable (range 6.4–291.6 g), but no systematic difference was found between the volunteers in this regard. Similarly, the cumulative faecal excretion of ^{26}Al over the 6 day collection period following the administration of each test solution was similar for both volunteers (mean mass of faeces excreted following each administration: volunteer A, 842 g per administration; volunteer B, 733 g per administration). In both subjects the faecal excretion of the unabsorbed ingested radionuclide was essentially complete by 6 days post-administration for all test solutions. Consideration of the cumulative ^{26}Al recovery over 6 days following each administration suggests a small systematic error in the analysis: an average of 120.7 Bq ^{26}Al was recovered following the ingestion of ^{26}Al-labelled aluminium hydroxide, compared with an estimated administered dose of 117.1 Bq, while an average 122.9 Bq was recovered following ingestion of the ^{26}Al-labelled aluminium citrate, compared with the estimated intake of 112.1 Bq. However this error, which is consistent with the accuracy of the techniques employed, is insignificant and has a negligible effect on assessments of aluminium retention in the gut.

Differences were found between the patterns of excretion of ^{26}Al in the volunteers. Figure 1 shows that volunteer B retained aluminium in the gut for 1–2 days longer than did volunteer A, e.g. most of the administered dose of aluminium citrate was voided during the first day by A, but in B little or no excretion by this route had occurred by this time. It follows that the higher ^{26}Al occupancy in volunteer B, expressed as Bq·day (Table 1), might be expected to result in a higher potential for bio-absorption in this subject. In both volunteers aluminium administered with citrate was retained within the gut longer than when administered as aluminium hydroxide alone. Since both volunteers voided similar masses of faeces, it is possible that retention is a function of ion adsorption into the gut wall, which may have been more marked in subject B and following intake of more soluble forms of aluminium.

Table 1. Total faecal excretion and occupancy of ^{26}Al in the gastrointestinal tract

	Fresh weight faeces (g)	^{26}Al (Bq)	^{26}Al occupancy (Bq·day)
Volunteer A			
hydroxide	715.0	116.8	272
hydroxide with citrate	1148.1	124.9	171
citrate	661.7	124.7	149
Volunteer B			
hydroxide	671.8	124.3	430
hydroxide with citrate	691.6	116.7	334
citrate	834.9	121.2	359

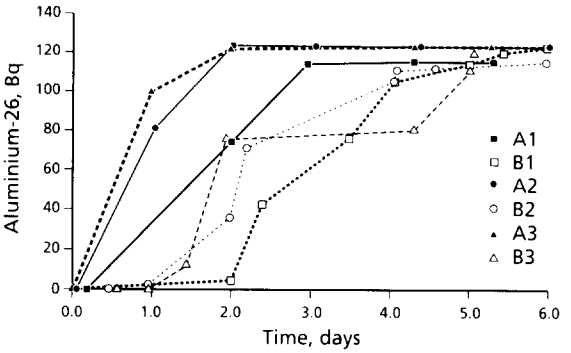

Figure 1. Cumulative faecal extretion of ^{26}Al. Values are given for times up to 6 days post-administration of either ^{26}Al-labelled aluminium hydroxide (1), aluminium hydroxide in the presence of stable citrate (2) or aluminium citrate (3).

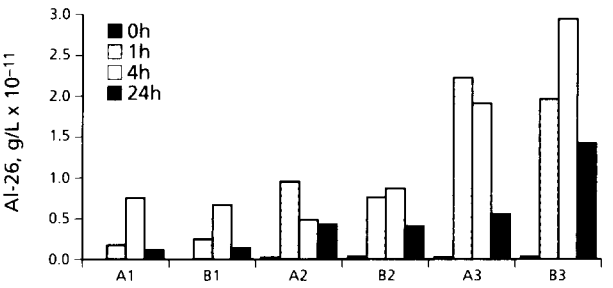

Figure 2. Blood concentrations of ^{26}Al. Pre-intake and post-intake values are presented for subjects A and B following the administration of either labelled aluminium hydroxide (1), aluminium hydroxide with citrate (2) or aluminium citrate alone (3).

Blood

The results of the blood analyses are presented in Figure 2. These show that following the administration of the ^{26}Al-labelled aluminium hydroxide alone, peak blood concentrations of ^{26}Al were detected at 4 h post-administration, reaching about 8×10^{-12} g l^{-1}. At this time most aluminium would have been present in the stomach or upper small intestine. For this test solution no marked differences were noted between the blood concentrations of the radioactive aluminium in the two volunteers. In contrast, following the administration of ^{26}Al-labelled aluminium citrate or the labelled hydroxide in the presence of citrate, marked temporal differences were found in the pattern of ^{26}Al transfer to blood. For both test solutions, ^{26}Al concentrations were highest at 1 h post-administration in volunteer A and at 4 h post-administration in volunteer B.

The results showed that, of the forms tested, ^{26}Al given

Table 2. Cumulative excretion of ^{26}Al in urine

	Time to last voiding (days)	Urine volume (l)	^{26}Al excreted (g)
Volunteer A			
hydroxide	5.9	15.0	1.02×10^{-11}
hydroxide with citrate	6.0	12.6	1.23×10^{-10}
citrate	6.0	13.7	4.49×10^{-10}
Volunteer B			
hydroxide	6.0	14.6	1.45×10^{-11}
hydroxide with citrate	5.9	13.0	1.99×10^{-10}
citrate	6.0	14.4	7.4×10^{-10}

as labelled aluminium citrate resulted in the highest blood ^{26}Al concentrations. It is also evident that the co-administration of the stable citrate solution with the aluminium hydroxide resulted in increased uptake of the radionuclide into the blood stream. Moreover, compared with the temporal pattern of ^{26}Al uptake following the hydroxide its uptake in the presence of citrate is delayed—more so in volunteer B which also showed delayed faecal excretion of the unabsorbed material. These data suggest that aluminium levels in the blood reach no convenient and consistent effective plateaux, and that bioavailability cannot be accurately determined from blood ^{26}Al or ^{27}Al levels at a single time after administration.

Urine

The volumes of urine collected from each volunteer are given in Table 2—these were essentially the same for both volunteers. The patterns of aluminium excretion following the administration of each form of ^{26}Al is shown in Figure 3. Following the administration of all labelled aluminium species, urinary excretion was greatest during the first day post-administration followed by a rapid subsequent decline in excretion levels. These falls were sharpest for the excretion of ^{26}Al following its ingestion in the form of the citrate and in this case the rate of fall, particularly in subject A, was very similar to the rate found following the injection of ^{26}Al-labelled citrate in a previous study. It follows that most of the ingested aluminium was rapidly absorbed into the blood stream of this subject. In volunteer B, uptake was apparently slower, consistent with a time delay in the uptake of some of the radionuclide. A similar delay was much more marked in both subjects following the ingestion of the ^{26}Al-labelled aluminium hydroxide, where a time delay of several days was indicated for most aluminium uptake in subject B. The pattern of ^{26}Al excretion following the co-administration of labelled aluminium hydroxide and stable trisodium citrate was similar to that found following the administration of the labelled citrate and, given the overall increased excretion levels following the co-administration of the citrate, suggests that the major effect of the citrate is to raise the bioavailability of the ^{26}Al locked within the hydroxide early in the digestive tract.

The mean cumulative levels of ^{26}Al excreted in the urine during the 6 days following each administration are given in Table 3 and Figure 3. The corresponding calculated levels of ^{26}Al uptake, assuming 72% excretion of absorbed aluminium, are also given in Table 3. These show that in both volunteers when ^{26}Al was given as aluminium citrate about 50 times more of the isotope was excreted in urine than when it was given as aluminium hydroxide and that the co-administration of the same quantity of citrate with the labelled aluminium hydroxide resulted a 13 times increase in ^{26}Al excretion in urine. These also show that urinary excretion of ^{26}Al by volunteer B was an average of 1.6 times greater than by volunteer A—an enhancement which is of the same order as the ratio of the average ^{26}Al occupancies in the gastrointestinal tract for these subjects, i.e. 2. It follows, that to a large extent the greater uptake of aluminium by B might be explained by the longer residence time of the aluminium in the gut of this volunteer.

Absorbed fractions

Absorbed fractions (f_1) for ^{26}Al following its administration as either labelled hydroxide, hydroxide in the presence of citrate or citrate are given in Table 4. These were calculated using the nethods employed by Day *et al.* (1991) and Edwardson *et al.* (1993), the blood ^{26}Al concentration data, as measured at either 1, 4 or 24 h after injection, and the blood volumes calculated for each volunteer. As expected, it can be seen that the results are inconsistent, with higher f_1 values at 4 h than at 1 h in some cases, but the reverse in others and with higher uptakes of an aluminium species indicated for volunteer A using some time data, but for volunteer B using others. Moreover, the differences indicated between the levels of ^{26}Al uptake from the different species (maximum 10 times) is much lower than the measured variations as indicated by the ^{26}Al levels in urine. These observations suggest that bioavailability results based on incomplete blood data are prone to considerable error.

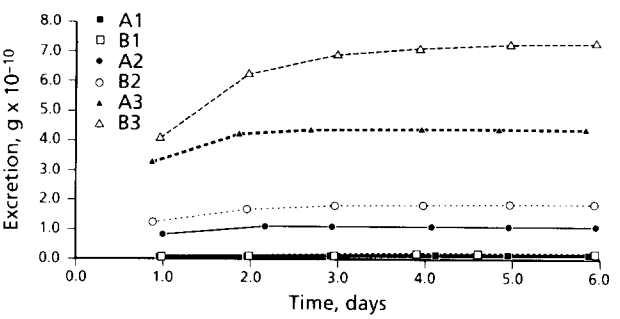

Figure 3. Cumulative urinary excretion of ^{26}Al. Data are presented for volunteers A and B following the administration of either labelled aluminium hydroxide (1), labelled aluminium hydroxide in the presence of stable citrate (2) or labelled aluminium citrate alone (3).

Table 3. Absorbed fractions for ^{26}Al calculated using urinary excretion data

	Cumulative ^{26}Al mass excreted (g)	Estimated ^{26}Al intake[a] (g)	f_1 (absorbed fraction)
Hydroxide			
A	1.02×10^{-11}	1.42×10^{-11}	8.61×10^{-5}
B	1.45×10^{-11}	2.01×10^{-11}	1.22×10^{-4}
mean	1.24×10^{-11}	1.72×10^{-11}	1.04×10^{-4}
Hydroxide + citrate			
A	1.23×10^{-10}	1.71×10^{-10}	1.04×10^{-3}
B	1.99×10^{-10}	2.76×10^{-10}	1.67×10^{-3}
mean	1.61×10^{-10}	2.24×10^{-10}	1.36×10^{-3}
Citrate			
A	4.49×10^{-10}	6.24×10^{-10}	3.95×10^{-3}
B	7.40×10^{-10}	1.03×10^{-9}	6.52×10^{-3}
mean	5.95×10^{-10}	8.26×10^{-10}	5.23×10^{-3}

[a]Calculated assuming 72% excretion of absorbed ^{26}Al in urine.

Table 4. 'Absorbed fractions' estimated from blood ^{26}Al content at either 1, 4 or 24 h post-administration

	1 h	4 h	24 h
Volunteer A			
hydroxide	5.8×10^{-5}	2.5×10^{-4}	3.7×10^{-5}
hydroxide with citrate	3.1×10^{-4}	1.5×10^{-4}	1.1×10^{-4}
citrate	7.4×10^{-4}	5.6×10^{-4}	1.8×10^{-4}
Volunteer B			
hydroxide	7.7×10^{-5}	2.1×10^{-4}	4.5×10^{-5}
hydroxide with citrate	2.3×10^{-4}	2.6×10^{-4}	1.2×10^{-4}
citrate	6.2×10^{-4}	8.3×10^{-4}	4.5×10^{-4}

Absorbed fractions calculated using the ^{26}Al in urine data following the administration of each species are given in Table 3. The estimated absorbed fractions (f_1) are:

^{26}Al as labelled aluminium hydroxide	1.04×10^{-4}
^{26}Al as labelled aluminium hydroxide with citrate	1.36×10^{-3}
^{26}Al as labelled aluminium citrate	5.23×10^{-3}

Discussion

The study described is a radioactive tracer study. In all such studies, the assumption is made that the body is unable to differentiate between stable and radioactive isotopes of the same element and that as a consequence they behave identically in the body. For bioavailability studies it is further assumed that the fraction of radioactive isotope absorbed will be the same as the fraction of stable isotope carrier. This will be true provided that all isotopes are speciated in the same way. The method of test solution/suspension production employed in the present study was deliberately chosen to ensure that radioactive isotope and stable carrier were speciated in the same way.

Reliability of method

To date, all ^{26}Al, and many stable aluminium, bioavailability studies have employed blood or plasma aluminium determinations, often at fixed single time points, to estimate gut uptake factors (Edwardson *et al.* 1993, Day *et al.* 1994). The results of our studies, to date, demonstrate the difficulties in this approach:

- Blood aluminium levels are lower than equivalent urine values and are, therefore, more difficult to measure (Priest *et al.* 1995a, Talbot *et al.* 1995).
- Blood aluminium levels following gastric uptake reach no convenient plateau for measurement purposes.
- Aluminium uptake may be protracted over several days.
- The kinetics of gut uptake is subject to significant inter-volunteer variability with evidence to suggest that some aluminium may reversibly bind to the gut wall.
- The kinetics of uptake is different for different aluminium species.
- Evidence exists to suggest that blood aluminium is rapidly diluted within a larger tissue fluid pool (Priest *et al.* 1991).

Therefore, it is not surprising that, in this study, it was not possible to reproduce urine-derived gut uptake factors using blood data generated for any time point post-intake. Moreover, the spread of blood-derived gut 'uptake values' measured in this study is considerably smaller than the spread indicated using urine data. For example, the maximum indicated difference between the bioavailability of ^{26}Al administered as citrate and as the hydroxide using blood data was 10, whereas the urine data shows aluminium given as citrate to be 50 times more bioavailable than when

given as the hydroxide. It is concluded that restricted blood data should neither be used to provide 'absolute' f_1 values, nor comparative f_1 data for different individuals, nor even comparative f_1 values for different aluminium species.

In contrast to the situation using blood data, when urine data, collected over 1 week post-administration, are employed to determine gut uptake the f_1 values derived are likely to be reliable. This is because most of the absorbed aluminium is excreted in urine during the first few days following intake (Talbot *et al.* 1995). The results of the present study show that even when aluminium uptake is delayed, a week's collection of urine is sufficient to derive a meaningful result. Nevertheless, some uncertainties exist due to inter-subject variability in the fraction of aluminium excreted in urine during the collection period (Talbot *et al.* 1995), but these are of much less significance than the unavoidable errors associated with the use of blood data and can be quantified. It follows that the suggested precision of the reported, urine-derived, gut uptake factors for each volunteer is about $\pm 10\%$ allowing for such inter-subject variability in excretion and that the mean for both volunteers is likely to be more precise. However, the present experiment used only two volunteers, consequently little information has been produced on the distribution of the bioavailability of any aluminium species within the population. Previous experience with other metals (e.g. lead) suggests that such inter-subject variations may be significant.

Calculated absorbed fractions

The present study was undertaken using two chemical species of aluminium. They were chosen because it was suspected that they would be either relatively bioavailable (citrate) or relatively non-bioavailable (hydroxide), in order to measure the likely range of aluminium bioavailabilities. All the substances tested are likely to be encountered in real life.

Citrate is a common component of many foods and drinks including citrus fruit juices. The gut uptake fraction calculated, using urine data, for aluminium ingested as an aluminium citrate solution in the present study is somewhat lower than a previously published level for the ingestion of similar species. In our study the calculated uptake, of about 0.5%, is a factor of 2 lower than that published by Day *et al.* (1991). However, Day's experiment involved a single volunteer and the quantity of citrate ingested was considerably higher. Moreover, the result was based on restricted blood data, the limitations of which are discussed above. Nevertheless, the present study indicates no reason why Day should have overestimated aluminium citrate bioavailability and it must be concluded that under some circumstances aluminium absorption must at least equal 1%. Furthermore, it is likely that aluminium bioavailability will depend to some extent upon a number of factors including the age (Barton 1987) of the subject (metal ion uptake in milk-fed infants is higher), the presence of food in the gut (food reduces metal bioavailability), the level of silicic acid in the diet (competitive binding) (Edwardson *et al.* 1993), the concentration of citrate (Partridge *et al.* 1992) and the ability of the gut wall to sequester aluminium in the gut lumen (Ganrot 1986). Despite these factors, experience with other polyvalent metal ions (Métivier *et al.* 1987) suggests that the 0.5% fraction measured in this study is likely to be close to the maximum aluminium bioavailability in older children and adults under normal ingestion exposure conditions—such as following the ingestion of aluminium in orange juice—and that the bioavailability of other, less soluble, ingested aluminium species, including aluminium hydroxide, will be lower. The measured result for aluminium hydroxide (absorbed fraction = 0.01%) is consistent with this suggestion.

While pure aluminium citrate is an unlikely food constituent, aluminium as aluminium hydroxide species is commonly ingested, it being the most likely species to form following the neutralization of aluminium in acid solutions and being a common pharmaceutical antacid preparation. In the latter form it may be consumed in multi-gram quantities over a protracted period. At first sight, the present results suggest that the consumption of aluminium hydroxide is unlikely to result in significant, compared with normal, excess body burdens of aluminium. This is because the gut uptake factor (0.01%) is very low and because only about 5% of that absorbed by normal healthy persons is likely to be retained by the body, i.e. 0.0005% retained (Priest *et al.* 1995a). However, aluminium antacids are commonly used in large quantities over long periods of time and also in renally compromised patients, as a phosphate binder, and under these conditions significant aluminium body burdens could arise, even with such a low normal retained fraction. Moreover, the present results show that the co-administration of citrate, a not uncommon medical practice, will result in even greater body burdens. The toxicological implications of these findings, with respect to antacids, is open to interpretation, particularly as the mass of aluminium hydroxide administered in the present study was unrealistically low for this type of exposure and at high mass intakes bioavailability may be lower. Also, freshly prepared aluminium hydroxide suspensions are more easily re-dissolved than aged preparations.

In conclusion, the results of the present study suggest that in common with other trivalent metals, aluminium is relatively non-bioavailable and that the consumption of either aluminium citrate or aluminium hydroxide in normal quantities is unlikely to result in toxicologically significant body burdens of this metal.

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