Human & Experimental Toxicology (1995), 14, 287–293

Human metabolism of aluminium-26 and gallium-67 injected as citrates

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1 ^{26}Al and ^{67}Ga were given as citrates to a healthy male volunteer by intravenous injection. The retention of both tracers was studied by body radioactivity measurement. Levels in blood and excreta were determined by γ-ray spectrometry and/or accelerator mass spectrometry.

2 More than half of the ^{26}Al had left the blood after 15 min and the decline continued, leaving <1% in blood after 2 d; the losses occurred both to renal excretion and through uptake by other compartments. Estimated excretion up to 13 d was 83% (urine) and 1.8% (faeces). Whole-body retention of 15% at 13 d declined to ~4% at 1178 d, when the daily reduction corresponded to a biological half-life of 7 y, suggesting that sustained intake of dietary aluminium may lead to a progressively increasing internal deposit.

3 The metabolism of ^{67}Ga differed markedly from that of ^{26}Al in all aspects studied.

Keywords: aluminium; gallium; injection; retention; excretion

Introduction

It has been estimated[1] that typically 35–40 mg aluminium is incorporated in the tissues of the adult person, mostly from the diet, but systematic studies of its biokinetic behaviour have been impeded through lack of a readily available radioactive tracer. Recent reviews[2–5] have concluded that the ingested metal is largely unabsorbed, that urinary excretion removes most of what is taken up, and that bone is the principal site of retention for the residue. This latter conclusion raises the possibility that sustained exposure may lead to a progressive increase with age in the body content of aluminium, in view of the slow turnover of other skeletally deposited trivalent metals.[4] In this account we report on the early biokinetics and long-term retention, studied by injecting a healthy male volunteer with the radioactive isotope ^{26}Al (half-life 7.16×10^5 y). We also report on the simultaneous behaviour of gallium in this subject, following injection of ^{67}Ga (half-life 78 h), addressing suggestions[6] that gallium is in certain respects a suitable metabolic tracer for aluminium.

Materials and methods

Selection of subject

The volunteer, Subject P, was a Caucasian male, of height 1.83 m, weight 77 kg and age 41 y, who gave informed assent following approval of the study by an ethics committee. There was no recent history of prescribed medication, and no use of any other pharmaceutical product during the 7-d periods preceding and following the injection. He had at no stage taken antacid preparations containing aluminium.

Preparation of radioactive tracers for injection

^{26}Al was produced by irradiation of magnesium with 49.6-MeV α particles. A carrier-free preparation of the radionuclide in a nitric acid solution was produced. The solution was evaporated to dryness and then dissolved in 0.01 M nitric acid with an equal volume of 2% (w/v) trisodium citrate. The resulting 1% aqueous citrate solution (pH 6.5) was passed through a 0.025 μm membrane filter; it was then sterilised by ultra-filtration and transferred to autoclaved vials. The contents of one such vial were tested for pyrogenicity. The solution from another was investigated by γ-ray spectrometry to determine its radiochemical purity and, by reference to the response to a suitable multi-radionuclide standard, the concentration of ^{26}Al.

The ^{67}Ga used was purchased as a sterile citrate solution, marketed as a radiopharmaceutical product.

Administration of tracers

3.5 mL of the ^{26}Al injection solution was drawn into a 5-mL syringe. A γ-ray spectrum was recorded from the loaded syringe, at a distance of 190 mm from a 150-mm-dia scintillation counter. The solution was then injected into an antecubital vein. The syringe was refilled to 3.5 mL with inactive carrier solution and recounted in the original geometry to allow cal-

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(Received 2 March 1994; accepted 18 May 1994)

culation of the fraction injected. The administered quantity was 0.51 kBq or c. 0.7 μg; the amount given was restricted by the cost and availability of the tracer, rather than by the anticipated committed effective radiation dose (0.13 mSv/kBq). The associated mass of trisodium citrate was 35 mg.

0.2 mL of the ^{67}Ga solution was drawn into a 1-mL syringe and injected 48 min after the ^{26}Al. Procedures analogous to those used for the ^{26}Al were adopted to determine the quantity injected (222 kBq, with 2 mg citrate).

Determination of tracers in blood

20-mL blood samples were taken at intervals (Figure 2) up to 880 d and transferred to pre-weighed vials.

Two methods were adopted to determine the ^{26}Al content of the blood. The early samples were placed intact between two shielded 150-mm-dia. NaI(Tl) scintillation counters; the response from coincident 511-keV positron annihilation quanta was recorded and compared with that from a standardised solution of ^{26}Al. The limit of detection was about 0.03 Bq ^{26}Al for a measurement time of 8 h and the radionuclide was detected in all samples withdrawn during the first 2 d. Subsequently, the ^{26}Al contents of *all* samples were determined by accelerator mass spectrometry (AMS), as follows. An aliquot of 1 mL was removed from each. 100 μg of stable aluminium (^{27}Al) was added as a yield tracer and the spiked samples were wet ashed with nitric and fuming nitric acids. The ash was dried and redissolved in 0.1 M nitric acid, 20 μL of which was spotted onto a sample plate, which was subsequently baked at 800°C to form an ion source. In this form, the samples were analysed with the tandem 17MV Van de Graaff accelerator and high-resolution magnetic spectrometer then operating at the Daresbury Laboratory. The detection limit for ^{26}Al is given as 10^{-18} g (c. 0.7 nBq).[7]

^{67}Ga in each of the samples up to 14 d was assessed from the γ-ray spectrum recorded with a semiconductor detector in well geometry.

Determination of tracers in excreta

All faeces were collected for 14 d after the injections. Voidings up to 4 d were processed and analysed individually; later voidings were combined, the bulked samples representing 1 or 2 days' output. The samples were ashed at 500°C and the ash was dispersed in a constant volume of thick gelatin solution which was poured into 100–mm-diameter plastic Petri dishes and allowed to set. The ^{26}Al content of each dish was determined by counting coincident annihilation quanta, with the same detectors as were used for the early blood samples. ^{67}Ga was assessed by γ-ray spectrometry with a 230-mm-dia. scintillation counter, with the source-detector distance 50 or 130 mm, depending on the activity present.

Urine was also collected for 14 d, but in the processing of the samples recovery of the tracers was incomplete and only roughly quantifiable at 70% from subsequent investigations. ^{26}Al and ^{67}Ga in the prepared samples, again as ash dispersed in gel inside Petri dishes, were nevertheless measured by the methods used for faeces.

Measurement of whole-body radioactivity

Measurements of whole-body radioactivity were made initially at daily intervals or more often, later much less frequently (Figure 1). The equipment comprised an array of six NaI(Tl) crystals, each 152 mm dia. × 89 mm thick, mounted four above and two below the supine subject, inside a room shielded on all sides by 100 mm lead.[8] The detection limit was 15 Bq ^{26}Al (3% of the injection) in a single 30-min measurement, based on the response from the 1.81-MeV γ radiation. The limit for ^{67}Ga, assessed from its photon emissions above 300 keV, was 100 Bq; this was small (0.05%) in relation to the intake, but radioactive decay of this isotope (half life 78 h) restricted the period of useful study to 21 d.

Investigation of distribution

The subject's content of ^{26}Al was insufficient to allow its distribution in the body to be studied at any stage. However, in the early stages the photon flux from the deposited ^{67}Ga was readily detected by a collimated scintillation counter scanning the posterior surfaces of the supine subject, and these investigations were conducted after 2 d.

Results: aluminium-26

Whole-body retention

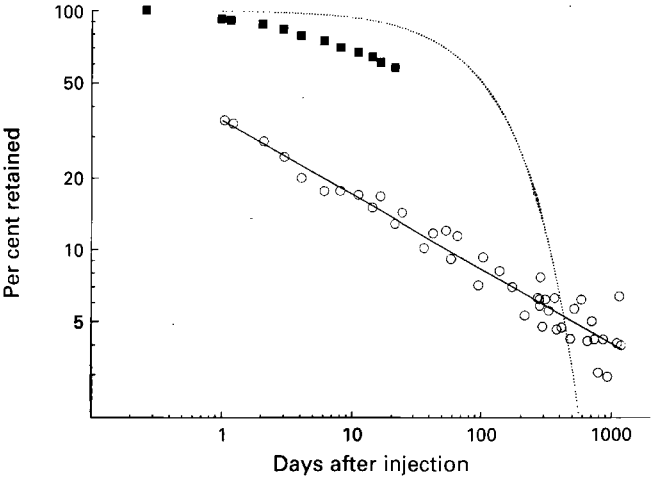

Figure 1 Whole-body retention of ^{26}Al (O) and ^{67}Ga (■). The solid line represents Equation 1; the broken curve is the single-exponential retention function for Al proposed by the ICRP[13].

The fractions retained in the whole-body are given in Figure 1, with both scales logarithmic. They are derived from the response attributable to ^{26}Al in each spectrum of whole-body radioactivity, compared with that recorded immediately after the injection. The scatter of the later points in Figure 1 is consistent with random statistical effects in radioactive decay. There may also be a small fractional error, probably no more than 5%, affecting all of the values plotted, arising from early changes in the distribution of the tracer affecting the efficiency of the whole-body counter. Beyond 24 h the effect of further changes is likely to be much smaller and Figure 1 should indicate reliably the rate of loss of the tracer remaining.

Figure 1 shows that about 65% of the injected ^{26}Al was lost in the first 24 h and that there was continued loss beyond that time, but that 4% of the intake has persisted in the body after 3 y. The essentially linear appearance of the data when plotted with logarithmic scales implies that the retention, R_t (percentage of injected activity at time t d after intake), can be represented by a power function of time. Such a function

$$R_t = 35.4\ t^{-0.32}\ (t \geq 1) \qquad (1)$$

provides an acceptable fit to the data for ^{26}Al in Figure 1, i.e. to the values after 1 d. Note that the incautious back-extrapolation of such functions can lead to unrealistic predictions; they increase without limit as $t \rightarrow 0$, and equation 1, for example, would predict $R > 100\%$ at times < 0.9 h. A feature of the power-function model is that daily excretion removes a progressively smaller fraction of the contemporary residue; the 'instantaneous half-life' T_t increases with time and is given by

$$T_t = \frac{t\ ln\ 2}{k} \qquad (2)$$

where k is the negative exponent (0.32 in equation 1). Hence, for Subject P, $T_t \sim 200$ d after 3 months and ~ 2400 d after 3 y.

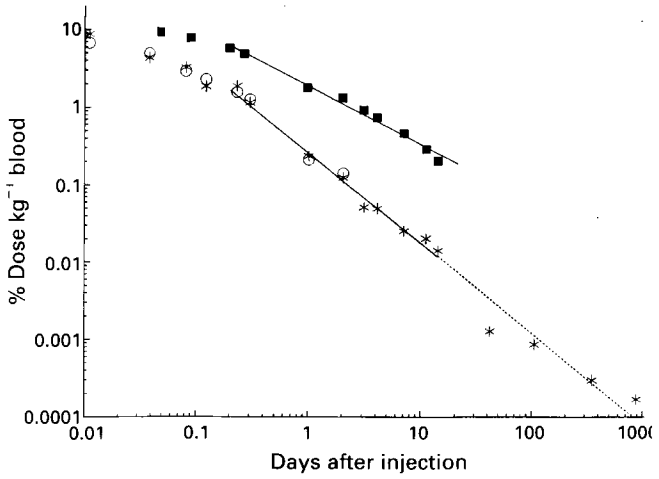

Figure 2 Concentrations of tracers in blood: O: ^{26}Al from coincidence γ-ray spectrometry. *: ^{26}Al from accelerator mass spectrometry. ■: ^{67}Ga.
Lines are equations 3 (^{26}Al) and 7 (^{67}Ga), fitted to data for 0.2–14 d.

Blood

Figure 2 shows the concentration of ^{26}Al in whole blood found in each of the first eight samples by γ-ray spectrometry, established by reference to the spectrum recorded with a standardised solution. The results for the 17 samples analysed by AMS, also shown, were provided as relative values; the data plotted were derived by tabulating the ratio of results by the two methods for each of the first eight samples, and applying the weighted mean of these ratios to all of the values from AMS. Normalised in this way, the two sets of data show consistent trends during the first 2 d, and those for 0.2–14 d can be represented by the function

$$C_t = 0.27\ t^{-1.18} \qquad (3)$$

in which C_t is the concentration (% of injection in 1 kg blood) at time t days.

The earliest result in Figure 1 is 7.8% kg^{-1} at 16 min (mean of values by the two methods). If the subject's total mass of blood was 5.7 kg, as indicated by a correlation with height and weight,[9] then about 45% of the injection would have been in blood at this stage. Based on equation 3, this would have declined to 0.7% at 2 d. Equation 3 does not accord satisfactorily with all of the later observations of C_t; it is seen in Figure 2 to overestimate the observed C_{42} (1.3×10^{-3} % kg^{-1}) by a factor of 2.5 and to underestimate the recorded C_{880} (1.7×10^{-4} % kg^{-1}) by almost a factor of 2. These discrepancies greatly exceed the estimated random experimental error (5%) in the data.

Separate measurements of ^{26}Al in the plasma and cellular fractions of the 880-d sample showed that at this stage about 14% was present in the cells.

Faecal excretion

Very little aluminium was excreted in the faeces, with <2 % cleared by this route during the first 13 d after injection (Table 1).

Urinary excretion

We have estimated the urinary excretion indirectly, as follows. Estimates of the cumulative total excretion at 24-h intervals were derived from 100-R_t, with R_t evaluated from Equation 1. The contemporary cumulative faecal excretion, from Table 1, was subtracted from each estimate, to give values for the cumulative urinary excretion at the end of each day; the output for each day was derived from successive values in this tabulation. These estimates are

Table 1 Levels of tracer in excreta

Period (days after injection)	Excretion of ^{26}Al (% of injection)		Excretion of ^{67}Ga (% of injection)	
	Urine	Faeces	Urine	Faeces
0 – 1	64	0.13	6.3	0.3
1 – 2	6.9	**0.83**	4.0	2.7
2 – 3	3.3	**0.18**	3.1	1.1
3 – 4	2.1	**0.02**	2.6	0.7
4 – 5	1.5	**0.11**	2.1	0.4
5 – 7	2.0	**0.13**	3.2	1.5
7 – 10	1.8	**0.08**	3.2	1.3
10 – 13	1.3	**0.30**	2.1	2.4
0 – 13	83	1.8	27	10.4

Faecal excretion is based on measured levels of tracer in processed samples.
Urinary excretion was estimated from reduction in whole-body retention, with allowance for faecal excretion.

shown in Figure 3, expressed as the excretion rate U_t (% of injection per hour averaged over the 24-h period, plotted at the mid-time t days of that period). They follow closely the power function

$$U_t = 0.47\ t^{-1.36} \quad (4)$$

which is shown as the fitted line in Figure 3.

Equation 4 is not guaranteed to represent U_t correctly at times << 1 d, for the same reasons as apply to equation 1 for R_t, from which it is derived; beyond 1 d, its accuracy will be limited principally by the possible systematic error, estimated at 5%, in the data of Figure 1. However, other data, included in Figure 3, support its validity for times > 0.2 d. These data are values of U_t based on the amounts of ^{26}Al recovered from the urine collections. They are seen generally to lie about 30% below the derived values, in satisfactory accord with the estimated losses during processing.

Estimated urinary excretion in successive periods of 24 h or longer is included in Table 1. That for the first day is based on the reduction in R (equation 1) during that time, while the subsequent values are derived by integration of equation 4.

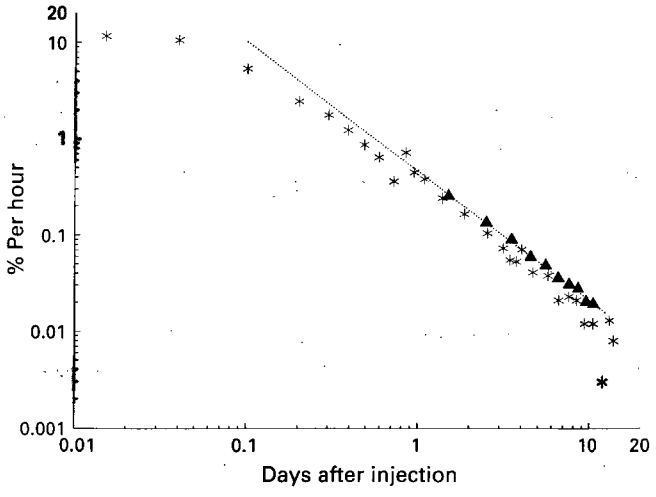

Figure 3 Urinary excretion rate of ^{26}Al. ▲: from whole-body retention and cumulative faecal excretion; the fitted line represents equation 4.
*: from amounts of ^{26}Al in processed urine collections, subject to incomplete recovery.

Excretory clearance rate

The total daily excretion rate (% d^{-1}), from differentiation of the whole-body retention function (equation 1), is given by

$$\frac{-dR}{dt} = 35.4 \times 0.32 t^{-1.32} (t \geq 1) \quad (5)$$

Equation 3 described the concentration of ^{26}Al in blood satisfactorily for $0.2 \leq t \leq d$ (Figure 2) and shows a reduction according to $t^{-1.18}$. Combining equations 3 and 5 leads to an expression for the excretory clearance rate from whole blood (ECR, kg d^{-1}) during their period of common validity (1–14 d):

$$ECR = \frac{-1}{C}\frac{dR}{dt} = 42t^{-0.14} \quad (6)$$

i.e. the ECR at 1 d was 42 kg d^{-1}, declining only slowly thereafter, to 29 kg d^{-1} at 14 d; since there was little faecal excretion, this was approximately the renal clearance rate also. The ECR cannot be assessed accurately at earlier times, for reasons which include the restricted blood sampling regime and the consequent difficulty of defining the variation of concentration with time during the rapid depletion occurring in the first few hours. There was evidence that the ECR between 0.5 and 3 h may have exceeded the value at 1 d, by which time the tracer would presumably be more typically distributed between the various aluminium-binding species in blood; however the elevation was a factor of two at the most.

Results: gallium-67

All data for ^{67}Ga are shown after adjustment for radioactive decay between injection and measurement, with an assumed half-life of 78 h.

Whole-body retention
Estimates from measurements up to 21 d are included in Figure 1, derived in the same way as those for ^{26}Al. As for ^{26}Al, a systematic error is possible because of early redistribution effects; the likely limit is 10%, somewhat greater than estimated for ^{26}Al because the photons from ^{67}Ga are subject to greater attenuation within the body. The loss of gallium was evidently much slower than of aluminium, with >50% retained after 21 d.

Distribution
The results of scanning with the collimated detector at 2 d were consistent with evidence[10] of an early distribution of gallium injected as citrate throughout all anatomical regions, with the liver and skeleton among the major sites of deposition after 24 h.

Blood
The ^{67}Ga was cleared from the blood less rapidly than the ^{26}Al (Figure 2), the power function giving the best fit to the concentrations after 0.2 d being

$$C_t = 1.84\ t^{-0.75} \qquad (7)$$

From equations 3 and 7, the percentage residue of ^{67}Ga after 2 d was some 10 times greater than that of ^{26}Al, with some 7% of the injected ^{67}Ga remaining. The two functions diverge, so that at 14 d the relative residue (Ga/Al) was 25.

Excretion
The loss of ^{67}Ga in faeces was much greater than of ^{26}Al (total 10.4% in 13 d, Table 1), although still minor relative to urinary excretion. The estimates of urinary excretion in Table 1 were derived on a basis similar to that for ^{26}Al.

Discussion

Behaviour of aluminium in blood
Less than 50% of the injection remained in blood after 15 min, and < 3% after 1 d. Losses occurred both to renal excretion and through uptake by other compartments. It is uncertain to what extent injection as citrate may in the short term have influenced the relative proportions removed by these routes, although there were no indications of a large and sustained effect in the early renal clearance rate. The slow decline in the later ECR implied by equation 6 appears likely to continue, since data summarised by Alfrey[1] indicate a normal clearance of only ~ 1 Ld^{-1} for the aluminium content of plasma.

Our data may have some relevance to the issue[11] of whether the rate of clearance from blood is affected by the concentration in plasma. Wilhelm *et al.*[11] refer to observations over 5 d after intravenous injection of patients with *c.* 2 mg Al, from which they deduced an apparent half-life in blood of 14 h; this implies a residue in blood of 0.26% at 5 d. Our equation 3, for a tracer quantity, indicates a similar residue of ~ 0.2% at that stage.

The speciation of Al in blood is uncertain. Rahman *et al.*[12] have suggested that most is bound to transferrin and this is supported by the observations of Day *et al.*[7] who also reported fractions associated with citrate and with a protein of low molecular weight. We have found a partial association with red blood cells, established at late times although possibly present also at a much earlier stage. This suggests a possible mechanism for long-term hepatic accumulation: the release of aluminium along with iron when blood cells break down in the liver.

Early excretion of aluminium
The results in Table 1 support indications[2] that systemic aluminium is lost mostly via the kidney and would appear to resolve controversy[11] over the importance of the biliary route. Possibly faecal excretion is important with large hepatic deposits, but for normal subjects our data support the assumption, common in bioavailability studies, that urinary output of aluminium is an adequate index of uptake from the gut.

These conclusions are reinforced by data from our subsequent (unpublished) studies in which six further volunteers received much smaller injections of ^{26}Al and the excretion of the tracer was measured up to 5 d. The result was 73 ± 7(s.d.)%, cf 79% from Table 1; again only about 1% was found in faeces. This agreement implies that Subject P was typical in his early clearance of aluminium injected as citrate and accordingly in the residue potentially available for long-term retention.

Long-term retention of aluminium
It is suggested[13] that systemic deposits of aluminium, including those in the skeleton, are cleared with a single half-life of 100 d. Figure 1 shows a quite different pattern. Initially, clearance was much more rapid than predicted,[13] but there were evidently compartments with much slower turnover, leading to a whole-body retention of 4% after 3 y.

The power function representation (equation 1) has been adopted solely as an analytical convenience. Its parameters probably have no specific metabolic significance. A similar pattern found in the retention of skeletal deposits of radium and other alkaline earth elements has been ascribed[14] to radial diffusion of metal ions through the calcified matrix surrounding canaliculi. However, a more likely explanation of the linear form in Figure 1 is that the combination of several exponential functions may approximate to a single power function,[15] and such a

combination often describes the whole-body retention of an element deposited in multiple independent or linked tissue compartments; the scatter and limited duration of the data in Figure 1 would frustrate useful attempts to evaluate initial compartment sizes and clearance half-lives for the pools responsible. In view of the very slow reduction after 3 y, the more tenacious residues are nevertheless likely to be skeletal, with their depletion possibly linked to bone turnover, which other studies[16] have suggested is normal in Subject P. To that extent it is likely that other subjects with normal stores of aluminium would exhibit patterns of long-term whole-body retention similar to that in Figure 1.

Accumulation of systemic aluminium

With certain assumptions, the data may be used to predict the long-term accumulation of aluminium in the body from normal environmental exposure. These assumptions are (i) that the pattern seen in Figure 1 is characteristic of the retention of systemic aluminium from dietary intake and (ii) that the biokinetics are unaffected by age at intake and by the burden attained; the latter in particular may not apply to elevated intakes of aluminium such as may arise from occupational exposure. It is also necessary (iii) to make assumptions as to the retention after the period of observation, currently 1178 d.

We first suppose that the power function behaviour (Figure 1) will continue indefinitely, i.e. the half-life of clearance T_t continues to lengthen with time according to equation 2. Integration of equation 1 gives an expression for the body content B_τ, as a function of time τ d after the start of exposure at a constant rate:

$$B_\tau = 0.52\ (\tau^{0.68} - 1) \qquad (8)$$

Here B_τ is expressed as a multiple of the daily systemic uptake. Insofar as equation 1 was invalid for $t < 1$, equation 8 will be incorrect at short times but after $\tau = 10$ d the error will be negligible. The integrated function increases without limit as τ increases, implying that equilibrium would never be reached between body content and daily intake; at $\tau = 20000$ d (55 y), its value is about 440. However, this approach will exaggerate the accumulation if, as is suggested, the linear appearance of Figure 1 results from the fortuitous combination of a series of exponential functions. In that event, the half life T_t will ultimately stabilise at that of the longest-lived component. Such an event would be marked by a systematic deviation of the observed values R_t from those indicated by equation 1. There is no indication of any such deviation in Figure 1 but let us suppose that it occurs at 900 d, when $T_t \cong 2000$ d (equation 2). The exponential function with a half-life of 2000 d leading to the value $R_{900} = 4\%$ is

$$R_t = 5.5\ e^{-0.00035t} \qquad (9)$$

Integration of equation 9 suggests that continuous exposure would after 55 y produce *in the compartment with longest half-life* a deposit of about 160 times the daily intake. This is likely considerably to underestimate the total accumulation because (i) it neglects the content of compartments with faster turnover ($T < 2000$ d) and (ii) components with half-life >> 2000 d are found in the retention patterns of other bone-seekers and are likely to exist in that of aluminium.

The data of Kaehny *et al.*[17] indicate a typical daily urinary excretion of 15 μg Al; this must correspond roughly to the daily systemic uptake, if our results (Table 1) are applicable. Applying the range of factors (160–440) derived above would suggest an accumulation during adult life of 2–7 mg, much less than published estimates of body content based on chemical analysis of tissues: 35–40 mg[1] and 60 mg.[18] Defects in our various assumptions may have contributed to this discrepancy but seem unlikely to be solely responsible. Possibly the reported analyses[1,18] were affected by contamination of the samples with aluminium in the general environment.

Gallium as a metabolic tracer for aluminium

Gallium is reported[6] to be a useful marker for the intestinal absorption of aluminium, but the metabolic similarities appear to extend no further. Gallium is subject to more prolonged retention in blood (Figure 1) and in the body as a whole (Figure 2), and faecal excretion of gallium (Table 1) is an important route of clearance, consistent with its deposition in the liver. These diverse clearance patterns make it unlikely that similarities in early tissue distribution found in the rat[6] have any relevance to man. The relatively slow clearance from the blood may indicate a stronger affinity for proteins such as transferrin, such as might be expected on the grounds of ionic size.

Acknowledgement

The study was funded by the Aluminum Association, Washington DC and by the International Primary Aluminium Institute, London.

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