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The bioavailability and metabolism of aluminium compounds in man

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Considerable concern has been expressed regarding the possible toxicity of Al in the body. In particular, many workers have speculated that this metal may be an important causative agent in Alzheimer's disease (e.g. McLachlan, 1991) as this disease is characterized by a dementia that is similar to dialysis dementia which is known to be caused by the accumulation of Al in the brain (Alfrey *et al.* 1976). It has been claimed that this speculation is supported by the results of a number of epidemiology studies linking the incidence of Alzheimer's disease with exposure to Al in drinking water. However, the power of these studies was generally low and the best of them, a French study, failed to demonstrate a link (Michel *et al.* 1991). Moreover, analytical studies conducted at the Harwell Laboratory (in collaboration with the Newcastle Medical Research Council (MRC) group) which use SIMS to demonstrate the presence of Al in brain tissues, show no consistent difference between the levels of this metal in normal and diseased brain tissues. Similar results have been obtained elsewhere and, although some groups still claim to be able to detect high levels of Al in the brain of dementia patients, most workers now agree that this metal is unlikely to be implicated in the causation of Alzheimer's disease.

However, Al is toxic at high concentrations within the body. The occurrence of dialysis dementia in renal patients, who accumulated high levels of Al due to its presence in the water used for dialysis is well documented, as are the occurrence of Al-induced bone disease (Klein *et al.* 1982; Visser & Van de Vyver, 1985) and microcytic anaemia (Elliott & McDougall, 1978) and the suppression of parathyroid hormone excretion (Cournot-Witmer *et al.* 1981). The occurrence of these 'high-level effects' has been reviewed by many authors including by De Broe & Van de Vyver (1985), Van de Vyver & Visser (1990) and Ward (1991).

In addition, impaired brain function has been claimed at lower concentrations in the body, for example as a result of the occupational exposure of gold miners to inhaled Al, McIntyre powder (Rifat *et al.* 1990), and in members of the general public following the Camelford accident in the UK (Edwardson, 1992). Also, dietary Al, as lactate, albeit at high levels, has been demonstrated to delay brain maturation in weanling rats (H. M. Wisniewski, personal communication) and to cause learning difficulties in young mice

(Yen-Koo, 1992). A link with low levels of exposure has also been claimed for some other conditions including heart disease (Elliott *et al.* 1978), osteoporosis and arthritis (Netter *et al.* 1981). Note, however, in the latter case a recent study conducted by AEA Technology and Liverpool failed to find a difference in the Al present in the femoral heads of normal and arthritic patients (Haines *et al.* 1993). To date no convincing evidence has been produced to either support or refute these claims of toxicity at low levels, but it would be reasonable to assume that some such effects do occur. In this respect it is important to point out that impaired cognitive function would be particularly difficult to demonstrate in Al-exposed populations, given the wide spread of cognitive function within the population and that in some populations exposure was under cognitive control. It follows that for this particular effect, and others, the need to establish the shape of the dose–response curve for known Al-induced disease is impelling and urgent.

METHODS OF UPTAKE AND BIOAVAILABILITY

Given the ubiquitous nature of Al in the environment (it is the third most common element in the earth's crust, amounting to an estimated 8% of its total mass) it is perhaps surprising that the human body contains only a few tens of milligrams and that the element has no known essential function. This low level results both from the insolubility, at neutral pH, of most natural Al compounds and from the protective barriers which the body's gut wall presents to prevent the uptake from food of metal ions in general and of non-essential ions in particular. Nevertheless, some Al overcomes these barriers and enters the body. While these levels are small for most environmental *Al* compounds such as aluminosilicate, the essential component of rock and soil minerals, they could be considerably greater for some manufactured compounds which may be of high solubility leading to increased uptake. This is a cause of concern to the leaders of the Al industry and to the users of Al compounds who are sensitive to the popular, and probably exaggerated, perception of their toxicity.

Metal ions enter the body by one of three main routes: via the gut wall, by inhalation and through wounds. All these routes may be important for Al. Probably the most important route is via the gut wall. It has been calculated that about 10–20 mg Al is present in the typical UK/USA daily diet, most being present in food (Pennington & Jones, 1989; Sherlock, 1989) such as some baked goods, beverages and water. For example, a recently published paper (Duggan *et al.* 1992) describes Al levels in some Al-canned cola and fruit juices which would constitute a significant proportion of the daily intake of this metal, up to 12 mg/d, in a person drinking three cans daily. However, by far the greatest proportion of ingested Al passes through the intestinal tract without being absorbed. By comparison with the bioavailability of other trivalent metal ions, including the lanthanide and actinide elements, which have been much studied because of their importance in the nuclear industry (ICRP, 1986), it may be predicted that only about 0·0001 of the insoluble species (such as aluminium oxides and aluminosilicates) will be absorbed. For the more soluble species much more may be taken up by the body. For example, a recent study of the bioavailability of ingested Al as ^{26}Al-labelled citrate (Day *et al.* 1991) indicated that as much as 1% of the metal may have been absorbed. This result is considered consistent with the ability of citrate, a common component of food, to complex metal ions, holding them in solution at physiological pH values when they would normally form less-bioavailable species. However, the results of this study

may be unrepresentative because of the large amount of citrate administered with the Al and because gastrointestinal absorption was only estimated, using blood Al levels, rather than measured in a full balance study. Another experiment conducted by the Newcastle MRC group estimated the uptake of Al following the addition of ^{26}Al to orange juice at normal citrate concentrations. This group is reported to have found much lower levels of Al uptake, but it is thought also to have based its results on blood values without access to measurements of the retention and excretion of Al from the body. On average it would seem that about 0·001 of the published daily Al intake in food is absorbed by the body. This proportion may be calculated by assuming a daily intake of Al of 15 mg, an excretion rate in urine of 25 μg/d (Triger & Singh, 1990) and 5% retention of Al in the body (Priest *et al.* 1991). This value is intermediate between the proportion of 0·0001 assumed for insoluble Al compounds and 0·01 estimated by Day *et al.* (1991) for aluminium citrate.

Unlike citrate, it is likely that the presence of silicic acid in food and drink will decrease the bioavailability of Al by providing a strong competitive binding site for it within the gut contents, thus making the metal less available for absorption through the gut wall (Birchall, 1991, 1992); note that some recent evidence suggests that citrate crosses the gut wall by a passive process, via spaces between cells, rather than through the cells themselves (Alfrey, 1992). In general it is unlikely that Al in food and drink, including water, presents any significant hazard. In contrast, the use of some Al compounds as antacids may present a small risk, as in this case the amount of Al ingested is many thousands of times larger than that present in food, typically several grams rather than 10 mg. Similarly, there could be a risk of Al toxicity when Al compounds are given to renal patients who are unable to excrete Al and who may, therefore, be expected to accumulate it within their bodies. Finally, the combined administration of Al compounds and citrate, for example as buffered Aspirin or as Scholl's Solution, may be expected to significantly enhance the uptake of the metal. However, even in these circumstances it is likely that, in most cases, insufficient Al crosses the gut barrier to cause serious health consequences.

While the gut wall presents a substantial barrier to the uptake of Al, the lung–blood barrier presents little, if any, obstacle. Inhaled aerosols are either exhaled, deposited in the nose, trachea and bronchioles, or are deposited within the alveolar tissues of the lung in amounts varying according to their size (ICRP, 1979). Particles deposited in the airways are mostly rapidly cleared and swallowed, presenting little chance for their dissolution and absorption, but material deposited in the alveolar region is not cleared mechanically. Instead it is engulfed by macrophages, which are the lung's scavenger cells, and is mostly retained until it is dissolved, whereupon it leaves the cells and enters the bloodstream; a few macrophages, with their particles, may migrate, via the lymphatic system, to the bloodstream; these will mostly deposit in the regional lymph nodes and liver. In general, the mass of Al-containing particles in the ambient atmosphere is small (estimated daily intake by inhalation is 4·4 μg) and many are likely to be either too large or too small for efficient deposition in the deep lung. Furthermore, most particles will be essentially insoluble and, therefore, add little to the body's Al burden. Consequently, under normal circumstances the uptake of Al by the inhalation route can be ignored as a significant source of body contamination. In contrast, some industrial aerosols, particularly those generated by operations of the Al industry and possibly including those generated in the exhausts of solid fuel rocket motors (such as those that power the space

shuttle on launch) may contribute to body Al levels in exposed workers. Indeed for many workers in alumina plants and in Al smelters this is the principal route of intake. Evidence supporting uptake by inhalation is provided by the high levels of urinary Al excretion by exposed workers (Ljunggren *et al.* 1991; Rockette & Gitleman, 1992). Similarly, under some conditions it is possible that under-arm antiperspirant sprays contribute to the body's complement of Al. This is because these sprays contain Al compounds. Moreover, a recent measurement made at the Harwell Laboratory of the spray generated by an own-brand can of a famous high street chemist showed it to be almost entirely composed of particles of about 1 μm in aerodynamic diameter which are ideally sized for deposition in the deep lung.

In addition, some workers in Canadian hard-rock, gold mines were deliberately exposed by inhalation to McIntyre powder, a mixture of finely divided Al and $Al(OH)_3$ (Bayerite and Gibbsite) powders at the end of each work shift in order to minimize the effects of silica inhalation. Evidence exists that some of these workers may have accumulated substantial amounts of Al in their lungs and bodies (Rifat *et al.* 1990). It is this population of workers that was the subject of the previously mentioned epidemiological study which claimed to demonstrate cognitive impairment as a consequence of Al exposure.

The uptake of Al through wounds is generally considered to be of little consequence except in two situations. First, and most importantly, Al compounds are used in many vaccine preparations, for example in the triple vaccine and in those used to desensitize hay fever sufferers. These are injected directly into the body and, therefore, circumvent all the body's protective barriers to entry. Moreover, multiple injections over a period of years could result in the accumulation of substantial local and systemic Al deposits. Second, the spraying of under-arm antiperspirants onto abraded skin produced during the process of razing axillary hair results in the intake of some Al: Freemont and his colleagues (Williams & Freemont, 1984) have described granulomas as resulting from this practice. Similarly, granulomas have been described following the injection of the triple vaccine (Savage, 1973). Other sources of wound uptake, such as the entry of Al-containing clays into cuts and grazes, are unlikely to add substantially to the body burden of this metal, even in the most adventurous of little boys.

BIOKINETICS RETENTION AND EXCRETION

The study of the behaviour of Al in animals and man has been substantially inhibited by the difficulty of measuring small levels of Al present within biological samples in an environment extensively contaminated with this element. This has made it impossible to rely on the results generated by many studies. In this regard it is notable that successive studies of the levels of Al in tissues tend to report lower levels with time, reflecting improvements in analytical techniques. In addition, as Al is a normal component of the body the interpretation of biokinetic studies of injected or ingested Al in man and animals is complicated by the investigator's inability to distinguish between Al from a test dose and that already present in the body. Most studies of stable Al are, thus, of poor sensitivity. Yet biokinetic findings on the retention and excretion of Al are vital in order to interpret human bioassay data, to determine the bioavailability of ingested and inhaled Al compounds, to determine the effectiveness of chelation therapy to remove Al and to determine the long-term consequences of acute and chronic Al intake.

Two main approaches have been taken to circumvent the problem. The first strategy employs the use of Ga commonly as the radioactive ^{67}Ga isotope, as a surrogate for Al. In vitro, the chemical properties of Al and Ga are very similar, it being very difficult to remove Ga from Al salts using chemical techniques. However, chemical reactions in the body, unlike in solutions, are very sensitive to ionic size and a recent study conducted at the Harwell Laboratory has demonstrated sufficient differences between the behaviour of these metals to invalidate many assumptions made on the basis of results obtained with Ga (Priest *et al.* 1991). The second approach, as used at Harwell, employs the radioactive isotope of aluminium ^{26}Al. This isotope can be detected at low levels in biological samples, using a range of techniques varying from γ-spectrometry to accelerator mass spectrometry (AMS), allowing the unambiguous identification of test, as opposed to endogenous, Al. ^{26}Al was injected into a human volunteer in a study supported by the Aluminium Association and International Primary Aluminium Institute and conducted by AEA Technology (Priest *et al.* 1991, 1992). Arguably, this single study provided more information on the biokinetics of Al, albeit in a single volunteer, than all previous studies, providing information not only on the excretion pattern of this metal but also information on its pattern of retention in blood and in the body generally.

The Harwell study showed that most Al is rapidly excreted in the urine within the first 48 h after its injection in a biologically active form, with about 80% excreted in the first 5 d after intake, unlike ^{67}Ga which was retained to a much greater extent. The study also showed that only a few per cent of Al are excreted in faeces, but that 30% of the excreted Ga was lost by this route. Ga was also retained in the bloodstream for much longer than Al, consistent with its lower level of excretion and its strong binding affinity for blood proteins. Also, while all the Ga was present in blood at short time-periods after injection, about half the Al was immediately lost. Given the rapidity of the loss and that the Al remained available for excretion, this was taken to indicate that the Al may have quickly established an equilibrium between that present in blood and that present in other tissue fluids. This is only likely to occur if Al is much less tightly bound to high-molecular-weight blood proteins, which are largely retained within the bloodstream, than is Ga. Using the AMS technique blood concentrations of ^{26}Al were measured for more than 100 d after injection. During this time the blood concentrations of the radionuclide fell by about five orders of magnitude. Also studied was the pattern of retention of Al in the body. The study showed that between 5 and 10% of the Al was retained in the volunteer. This being lost with a very long half-time. It is expected that ^{26}Al will be measurable in the body of the volunteer for many decades. These results are important because they clearly demonstrate that under constant intake conditions Al will accumulate in the body. For the volunteer in question it was estimated that after 50 years of exposure the Al body burden would be equal to about 460 times his daily intake of this metal or about 500 times the amount excreted daily in his urine.

BIOKINETICS: TISSUE DISTRIBUTION

Once Al gains entry into the bloodstream and tissue fluids it is available for binding to a variety of potential ligands including blood proteins and low-molecular-weight species. Of the blood proteins transferrin, the Fe-transport protein, is commonly cited as the most avid binder of Al (Trapp, 1983). In this way Al would ride 'piggy-back' on the

Fe-transport system within the blood. The role of low-molecular-weight species, including low-molecular-weight proteins and citrate, is less certain, with different authors claiming different fractions associated with these. However, a recent study indicated that as much as 50% of Al in the blood of normal subjects and dialysis dementia patients may be associated with low-molecular-weight species (Gonick & Khalil-Manesh, 1992), a result which is considered consistent with the observations made in the Harwell human volunteer study (Priest *et al.* 1991, 1992). Birchall & Chappell (1987) and Birchall (1991) have claimed that silicic acid in blood may also bind Al-producing aluminosilicates. Subsequently, Al is either excreted or is deposited in tissues.

Following their entry into the bloodstream, some metals quickly equilibrate with chemically similar metals in the body and become widely distributed. For example, Cs, a group 1 element with monovalent ions, equilibrates with other group 1 elements in the body including K. This becomes distributed throughout the body, showing no marked concentrations in specific tissues. In contrast, most metallic ions are deposited to a much greater extent than average in a few tissues. In this context, the most important tissues are the skeleton, liver and kidneys, although, the proportion of the total body burden deposited in any of these tissues is very variable and depends on many factors, including the element concerned and the age, sex, metabolic status and species of animal. Nevertheless, the major deposition site for many metals is the skeleton and it is for this reason that they are commonly referred to as bone-seekers. Such bone-seekers include not only obvious candidates such as Ca, and related metals, but also Fe, Pb, Cd, Zn, Pu, Zr and many others (Priest, 1990). All the available evidence suggests that Al is such a bone-seeker, the skeleton being its most significant site of deposition in the human body. Skeletal deposits of this element are easily detected using histochemical staining techniques (Denton *et al.* 1984; Verbueken *et al.* 1985).

Currently, there is little reliable evidence concerning the amount of soluble Al that deposits in the liver, but this would be the major site for the deposition of Al-containing particles such as those which may pass into the body via the lungs, gut or even skin. These particles will be essentially inert and will be retained or dissolved independently of other metabolized Al deposits. Measurements of total liver Al suggest values in the region of 6–9 mg for normal adults (Alfrey, 1980; Alfrey *et al.* 1980; Triger & Singh, 1990) and 4 mg in adults with liver disease (Triger & Singh, 1990). If correct, these would indicate that a significant proportion of body Al is present in this organ. However, the Harwell volunteer study (Priest *et al.* 1991, 1992) failed to identify liver Al deposits of this size. Moreover, a failure of Al to deposit in the normal liver would be entirely consistent with the low levels of faecal excretion found in the Harwell human volunteer study. It would also be consistent with the small size of the Al ion. Durbin (1962) at the Lawrence Berkeley Laboratory has shown that there is a progressive shift in the initial deposition pattern of trivalent elements in rats, which appears to be related to their ionic radius. The elements tested were the trivalent actinide and lanthanide elements which show a contraction in ion size with increasing number. This decrease, known as actinide and lanthanide contraction respectively, is associated with increased hydrolysis of the aqueous ions, with a decrease in the solubility of compounds and with a greater stability of complex ions (Durbin, 1973). Liver deposition is high and skeletal deposition is low for the lighter elements of larger ionic size, ranging from Ce (radius (R) 103 pm) to Gd (R 94 pm); whereas for the heavier smaller ions spanning Tb (R 92 pm) to Lu (R 84 pm)

skeletal deposition is high and liver deposition is low. Using the relationship demonstrated by Durbin in rats, Al (R 51 pm) would be expected to deposit almost exclusively in the skeleton. Nevertheless, caution should be expressed when extrapolating rat data to man as experience with many of the previously mentioned elements suggests that the proportion of an intake that is deposited in the human liver will be higher than that measured in rats (Priest, 1990).

Within the skeleton Al, in common with most other polyvalent metal ions, deposits on bone surfaces within a very thin layer. How metal ions deposit in this way is unclear, but three modes of uptake have been suggested. First, the metal may become trapped within the hydration shell of the bone mineral crystal, second it may become incorporated into new bone crystals as they are formed at sites of bone accretion or finally they may just become bound by acidic organic components of the bone matrix, such as phosphoproteins (Priest, 1990). Subsequently, Al will remain on the surface until that surface is remodelled. If the bone surface is growing then the Al will become buried often in bands which are easily detected by staining techniques. Conversely, if the bone surface is being eroded by bone-resorbing cells, osteoclasts, then the surface will be stripped of Al as it is resorbed and the Al is likely to become transferred to the osteoclasts, with elements of the resorbed bone matrix, where it will remain for a short time before it is transferred to macrophages in the bone marrow. While osteoclast deposits of Al have yet to be demonstrated their presence in marrow macrophages has been established using a variety of techniques including LAMMA (Van de Vyver & Visser, 1990). Moreover, the pathway described has been clearly identified for trivalent elements in the lanthanide and actinide series of the periodic table (Arnold & Jee, 1957). Later, probably over a period of several weeks or months, the Al will be released from the macrophages in a metabolically active, soluble form. This may then be expected to either redeposit on local bone surfaces or will re-enter the bloodstream for deposition elsewhere or, more likely, for excretion in urine. In this way small quantities of Al will be available for deposition in bone at all times after intake and all bone deposited during this period will be contaminated with the metal. It follows that the behaviour of Al in the skeleton is likely to be cyclic and consist of alternating deposition and removal steps. This cycle, as developed to describe the distribution of the bone-seeker Pu, is summarized by Priest (1990). Bone cycling may be expected to result in the maintenance of low levels of Al in the blood and urine at all times after its intake until it has been completely lost from the skeleton. As the rate of bone turnover is very low in adult man, accounting for only 3–20% of its total mass per year (depending upon the type and position of the bone), most Al will remain in the body for many tens of years, explaining the noted avid retention of some Al within the body of the human volunteer used for the Harwell study. In children and animals, which exhibit much higher rates of bone turnover, Al will be lost more rapidly.

It is axiomatic, that given a knowledge of the fate of Al entering the blood-supply and a knowledge of bone turnover, it is possible to predict its retention pattern in humans of different age and sex. The development of such metabolic models is a key step in interpreting the excretion data provided by Al workers and others exposed to this metal. Moreover, it should be possible at post-mortem examination to estimate the Al body burden of a cadaver by the analysis of appropriate bone samples. Indeed a current study, being conducted jointly by the Harwell Laboratory, Bristol University and the Water Research Council in the UK, is attempting to estimate regional variations in the Al

burden of children by the analysis of some of 12 000 collected teeth (an accessible and reproducible part of the skeleton) which were removed from children for orthodontic purposes, this technique having been successfully used to estimate Pu and Sr (Long *et al.* 1991), Pb and Cd (Stack, 1990*a*,*b*) burdens.

CONCLUSION

In summary, Al when present in the body at high concentrations causes a variety of diseases which have all been described in Al-contaminated renal patients, but at low concentrations causes no measured effects. Al is poorly absorbed by the body via the gut, but is likely to be more bioavailable following inhalation. Indications are that citrate enhances the gut uptake of Al, but that silicic acid renders it less bioavailable. Al uptake from vaccines, and following the protracted use of Al-containing antacids, are considered the most significant sources of body Al.

Following its entry into the bloodstream, most Al is excreted in the urine and only a little is excreted in faeces, but the 5% that is retained is deposited in the liver and skeleton in unknown proportions. Much of this is retained for many years. The most significant deposits are probably skeletal; Al deposits, within the skeleton, on bone surfaces. These surfaces may subsequently be either added to or resorbed, resulting in either the burial of Al deposits or their removal to osteoclasts respectively. Resorbed Al is subsequently released into tissue fluids for redeposition or excretion. Due to the retention of some Al in the body for many years no equilibrium will become established between Al intake and body content in man, and under constant-exposure conditions man will continue to accumulate Al.

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