Aluminium: gastrointestinal absorption and renal excretion

C. J. LOTE AND H. SAUNDERS
Department of Physiology, The Medical School, University of Birmingham, Birmingham, U.K.

INTRODUCTION: SOURCES AND BIOAVAILABILITY OF ALUMINIUM

Aluminium is the most abundant metal and constitutes 8% of the earth's crust. It is a normal constituent of vegetable and animal tissues and is present in raw untreated water. In domestic tap-water supplies, aluminium may be present in high concentrations either from its presence in raw water or, more commonly, as a result of its use during the water-purification process. Aluminium in the metallic form is widely used for both industrial and domestic purposes, and a variety of aluminium salts are used in foods, fluids, cosmetics and medications.

The toxicity of aluminium in patients with renal failure is now well documented, and dialysis encephalopathy, osteomalacia and anaemia are recognized hazards in such patients if aluminium is not excluded from dialysis fluids and medications. The safe levels of aluminium in food, water, medications and infusion fluids for subjects with normal renal function are unknown, but aluminium has been implicated as causative agent in a number of dementia diseases, including Alzheimer's disease.

There are a number of recent reviews of aluminium toxicity [1-5]. In contrast to these, in the present review, we concentrate on the mechanisms of absorption and excretion of aluminium, rather than the consequences of aluminium deposition in the body. The normal dietary source of aluminium is food and water to which aluminium has been added or in which there is naturally a high content [6, 7]. The normal daily intake of aluminium is estimated to be approximately 9 mg/day in teenage and adult females and 12-14 mg/day in teenage and adult males [7]. However, it has been stated that "the inappropriate choice of foods, methods of food preparation and non-prescription drugs can readily increase the daily intake of aluminium to several thousand mg each day" [8]. Such high aluminium intakes are particularly likely in individuals who ingest aluminium-containing drugs as antacids or phosphate-binders. Tea leaves contain relatively large amounts of aluminium, since tea plants accumulate aluminium from the soil [9]. Koch et al. [10] reported "that at least some of the aluminium present in tea is absorbed and that tea consumption must be considered in any assessment of the total dietary intake of aluminium in human beings". However, tannin, also present in tea, is an inhibitor of gastrointestinal aluminium absorption [10a], and hence the bioavailability of the aluminium in tea is relatively low.

Aluminium salts have a number of functions when used as food additives [8]. For example, the acidic forms of sodium aluminium phosphate are added to commercial cake mixes and self-raising flour as E541, where they act as leavening agents in reaction with sodium bicarbonate. The alkaline forms of these aluminium salts are added to processed cheeses as emulsifying agents.

Another source of aluminium is baby-milk powder. Freundlich et al. [11] reported that the aluminium content of a variety of milk powders that they analysed ranged from 124 to 351 μg/l, although values as high as 2346 μg/l have been reported in highly processed and modified milk powders [12]. The aluminium content of normal breast milk is 2–10 μg/l. Koo et al. [12] proposed that aluminium contamination of baby-milk powders was due to the use of raw materials such as soya bean, additives (for example calcium and phosphorus), manufacturing processes and the type of storage container.

The aluminium content of domestic water supplies is recognized as a potential major source of exposure for this metal ion in patients with chronic renal failure, since dialysis fluids may contain aluminium, and such patients may also be taking oral aluminium-containing drugs as phosphate-binders. The critical concentration of aluminium in dialysis fluid (above which there will be a significant net transfer of aluminium to the patient) is a matter of some debate, but ranges from about 14 μg/l [13] to 27 μg/l [14]; ideally, the dialysate aluminium concentration should be well below this. An epidemiological survey of haemodialysis patients, indicated that those who were
absorption are listed in Table 1, and provide clues to the physiological processes involved.

Physicochemical factors. The solubility of aluminium salts in aqueous solution is complex, and is influenced by pH and by other ionic species [26].

In acidic solutions (below pH 4), aluminium in solution is found as Al(H₂O)₅³⁺, often written in an abbreviated form simply as Al³⁺. This Al(H₂O)₅³⁺ can form colloidal aluminium–polyoxo complexes at pH values over 4, but these redissolve if the pH is lowered or raised, since in alkaline solutions aluminium is again soluble as Al(OH)₃. Free Al³⁺ is decreased by the presence of phosphate, which forms insoluble salts. In contrast, citrate enhances the solubility of Al³⁺, and at pH 2–5 a neutral soluble citrate–aluminium complex exists [26, 27].

How do the above facts relate to aluminium absorption? There is considerable evidence that citrate enhances the intestinal absorption of aluminium [29–32], and this effect is largely attributable to the formation of the soluble citrate–aluminium chelate. However, citrate may have additional effects on aluminium absorption, either by facilitating transcellular absorption or by opening the tight junction and enhancing the paracellular movement of aluminium [33]. Citrate is known to open epithelial tight junctions in cultured cells [34], and this finding has been supported by work on proximal (rat) jejunal segments in Ussing chambers [21].

The interactions of citrate with calcium are also likely to have effects on aluminium absorption. Calcium inhibits the absorption of aluminium, and thus more aluminium will be absorbed from water with a low calcium concentration. These observations suggest that the mechanism of aluminium uptake in the gut may share some features of the calcium absorption process [35, 36]. In isolated rat jejunal slices, aluminium uptake was reduced by calcium-channel blockers and increased by calcium-channel activators [37]. These findings raise the possibility that the effects of citrate on aluminium absorption may involve calcium. Citrate is an effective chelator of calcium, and in the renal proximal tubule such complex formation inhibits citrate and calcium absorption [38]. In the gut, similar complexation of calcium with citrate may make calcium unavailable for absorption, thereby enhancing aluminium absorption. However, it is not entirely clear why citrate may inhibit calcium absorption but facilitate aluminium absorption.

There are also antagonistic interactions between aluminium and fluoride absorption in the gut. Ingestion of aluminium hydroxide decreases the intestinal absorption of fluoride [39]. High aluminium and low fluoride concentrations in the water supply for dialysis patients increases the incidence of encephalopathy and bone fractures [40]. Related to these findings is the observation from an epidemiological study [41] that in areas where domestic tap water was highly fluorinated, there were fewer reported cases of Alzheimer's disease compared with areas with low fluorinated water. Aluminium (Al³⁺) forms strong complexes with F⁻ [26]. The above findings
imply that such complexes, if formed in the gut, are not readily absorbed. Silicic acid \([\text{Si(OH)}_3]\) has a strong affinity for aluminium. A recent report has indicated that the silicic acid content of water has a major effect on the bioavailability of aluminium, with aluminium bioavailability decreasing with increasing silicic acid content [42]. The same authors suggest that this could occur in the gut as a result of the formation of hydroxy-aluminosilicates [43].

There is persuasive evidence that aluminium can substitute for iron in a number of sites in the body [44, 45], and several research groups have investigated the possibility that the mechanisms of iron absorption from the gut may be involved in aluminium absorption. The mucosal cells of the small intestine (primarily the duodenum) take up iron, and it is bound intracellularly to a protein, apoferritin, to form ferritin. Some of the iron enters the plasma where it is bound to the protein transferrin. Aluminium can be bound by both ferritin and transferrin. It is likely that the aluminium which binds to ferritin in the mucosal cells is largely not absorbed into the plasma, but remains bound and is eliminated from the body when the cells are shed into the intestinal lumen. Whether iron in the intestinal lumen influences aluminium absorption is a question which cannot be answered with certainty at present. Van der Voet & de Wolff [46] concluded that \(\text{Fe}^{2+}\) reduced aluminium absorption, whereas \(\text{Fe}^{3+}\) had no effect. Cannata et al. [47] proposed that the mechanism for intestinal absorption of aluminium might involve a 'common pathway' for metal ions including iron, since they found that iron uptake by ferritin prevented aluminium absorption. However, Blachr et al. [48] found that iron in the intestine stimulates aluminium absorption. A variety of metal ions can bind to transferrin, but they do not bind to the iron-binding site. It may be that \(\text{Fe}^{2+}\) has an allosteric effect on the transferrin molecule, preventing aluminium from fitting its binding site. The interrelationships between iron and aluminium absorption remain confused. There is also some evidence for a negative interaction between aluminium and sodium during intestinal absorption [49].

**Physiological and pathophysiological factors.** Parathyroid hormone (PTH) increases the gastrointestinal absorption of aluminium [50, 51]; in patients with renal failure who were not on dialysis or receiving aluminium-containing phosphate-binders, those patients who developed osteomalacia had high serum PTH levels (3.1 ± 1.4 ng/ml compared with a normal value of less than 0.5 ng/ml), with the implication that this led to increased dietary aluminium absorption [52]. However, it is reported that in uraemic rats, in which gastrointestinal aluminium absorption is enhanced (see below), PTH does not further increase aluminium absorption [53].

In addition to the above reports of effects of PTH on aluminium absorption, there are also reports that aluminium depresses PTH release [54].

Burnatowska-Hledin et al. [55] have shown that 1,12-dihydroxyvitamin \(\text{D}_3\) increases the gastrointestinal absorption of aluminium, a finding which, like the PTH data above, supports the view that aluminium and calcium absorption may have related mechanisms.

The kidneys are the main route of aluminium excretion, and consequently the gastrointestinal absorption of aluminium is of great importance in patients with compromised renal function. There is evidence that uraemia per se increases gastrointestinal absorption of aluminium in man and the rat [56, 57]. Uraemic children also have an increased incidence of aluminium loading and toxicity [58], perhaps because they need large doses of phosphate-binders relative to body weight; and the effects of uraemia and citrate on aluminium absorption appear to be synergistic [21]. Fig. 1 illustrates the factors which influence gastrointestinal absorption of aluminium.

**Fate of absorbed aluminium**

What happens to the fraction of dietary aluminium which does enter the plasma? Aluminium binds to plasma proteins, mainly to the iron-binding protein transferrin and to albumin [44]. There are wide variations in the reported values for the extent of aluminium binding to protein; the range is 8% [59] to 98% [60]. Although the former of these studies was in man, and the latter in the rat, nevertheless species variation seems to be of minor importance. Much more important is the methodology used to assess binding. In general, the findings are based on ultrafiltration experiments. Gidden et al. [59] have demonstrated that the ultrafilterability of plasma aluminium depends on aluminium concentration, i.e. increasing the aluminium concentration decreases aluminium

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**Table 1. Factors affecting aluminium absorption**

<table>
<thead>
<tr>
<th>Physical factors</th>
<th>Silicic acid</th>
<th>Iron</th>
<th>Fluoride</th>
<th>pH</th>
<th>Calcium</th>
<th>PTH</th>
<th>1,12-Dihydroxyvitamin (\text{D}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on aluminium absorption</td>
<td>Enhances</td>
<td>Inhibition</td>
<td>? (see the text)</td>
<td>Inhibition</td>
<td>Changes from neutral enhance absorption?</td>
<td>Enhances</td>
<td>Enhances</td>
</tr>
</tbody>
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**Table 2. Factors affecting aluminium absorption**

<table>
<thead>
<tr>
<th>Physical factors</th>
<th>Citrate</th>
<th>PTH</th>
<th>1,12-Dihydroxyvitamin (\text{D}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on aluminium absorption</td>
<td>Enhances</td>
<td>Enhances</td>
<td>Enhances</td>
</tr>
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**Table 3. Factors affecting aluminium absorption**

<table>
<thead>
<tr>
<th>Pathophysiological factors</th>
<th>Uraemia</th>
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<tbody>
<tr>
<td>Effect on aluminium absorption</td>
<td>Enhances</td>
</tr>
</tbody>
</table>
Gut lumen

Aluminium

Organic
relatively insoluble

Inorganic

\( \text{Al}^{3+} \)

absorption

Enhanced by:

1,2-Dihydroxyvitamin D

1,25-Dihydroxyvitamin D

Inhibited by:

calcium

tannin

fluoride

Complex with iron-binding protein ferritin

Return to gut lumen when cells sloughed off

Faecal excretion

Fig. 1. Gastrointestinal absorption of aluminium.

Plasma aluminium

80–95% protein-bound
(mainly to transferrin)

5–20% soluble
(alumino-silicates)

Tissue uptake

Binding to

ATP

Cyclic GMP
[73]

Cyclic AMP
[73, 74]

Inositol phosphates
[42, 77]

Disruption of

Biopterin metabolism
[72, 73, 75]

Gene transcription

Interference with cell signalling

Inhibition of caffeine-sensitive \( \text{Ca}^{2+} \)-channels [76]

Fig. 2. Some effects of absorbed aluminium.

ultrafilterability. This finding has been essentially confirmed in many other studies (for example, [20, 60–62]).

It is unlikely that the ultrafilterable fraction of plasma aluminium represents a single form of aluminium, since there are a number of low-\( M_r \) binders of aluminium in plasma, including citrate, fluoride, phosphate, bicarbonate and silicates. Fig. 2 shows some of the effects of absorbed aluminium.

RENAL EXCRETION OF ALUMINIUM

Urinary aluminium excretion increases after oral aluminium loading in subjects with normal renal function [63]. The \( M_r \) cut-off of the renal glomerular filter is 70 000 (e.g. [64]). Consequently, transferrin \( (M_r 77 000) \), the main aluminium-binding protein in plasma, is not filtered. Hence it is likely that only a small fraction of plasma aluminium will be filterable, although as the preceding section indicates, this fraction will be variable, depending on the plasma concentration of aluminium. The aluminium clearance is normally less than 5% of the glomerular filtration rate in individuals with normal renal function.

The dangers of aluminium toxicity were initially recognized in patients with renal failure, who were receiving dialysis treatment. ‘Dialysis dementia’, an encephalopathy occurring in renal dialysis patients, was first described in 1972 [65], and was found to be associated with the accumulation of aluminium in the brain [66]. The recog-
nition of this condition led to many more reports of aluminium-related dementia in renal patients. Other pathological features, including vitamin D-resistant osteodystrophy, were also evident in such patients and the condition, first recognized in Newcastle-upon-Tyne (U.K.), was termed 'Newcastle bone disease'.

The above conditions are caused by aluminium entering the blood and being deposited in the body tissues, deposition in the brain leading to encephalopathy, and deposition in bone leading to osteodystrophy. In the renal failure patients there were two sources of this aluminium: (1) the water used for dialysis, and (2) dietary aluminium hydroxide used as a phosphate-binder in such patients. The obvious question is whether the aluminium toxicity was due to impaired excretion consequent upon the renal impairment, or to excessive amounts of aluminium entering the plasma by bypassing the gut barrier (or both).

Because of the complex relationship between protein-binding of aluminium, and the plasma aluminium concentration, it is difficult to assess quantitatively the role of the kidney in aluminium excretion. Renal aluminium clearance decreases with increasing plasma aluminium concentration [60, 62, 67]. However, since plasma aluminium concentration in healthy subjects is low, 10 μg/l or less, it seems likely that the kidneys play an important role in aluminium excretion.

Little is known of the renal tubular handling of aluminium, and this is a question we are currently investigating. Work by Galle [68] has indicated that, after filtration, aluminium is reabsorbed by the renal tubule cells and is bound intracellularly to phosphates and proteins [60, 69]. There is also evidence of distal tubular secretion [70].

From time to time, incidents of high aluminium exposure occur (e.g. in Camelford, Cornwall, U.K., where aluminium sulphate was added in high concentration to drinking water in July 1988). Clearly, if we had greater understanding of the renal mechanisms involved in aluminium excretion, this might increase the possibility of improving aluminium clearance. If renal transport mechanisms for aluminium resemble those in the gut, then drugs or procedures which modify for example calcium absorption (see, for example, [71]) might be useful in modifying aluminium absorption. Clearly, this is an area in which more research is needed.

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28. Reference deleted.


Gastrointestinal absorption and renal excretion of aluminium


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