Renal Handling of Aluminium

D.G. Shirley^a C.J. Lote^b^aDepartment of Physiology and Centre for Nephrology, University College London, London, and^bDivision of Medical Sciences, University of Birmingham, Birmingham, UK

Key Words

Aluminium excretion · Aluminium filterability ·
Aluminium reabsorption · Citrate · Micropuncture

Abstract

Aluminium (Al) is absorbed from a variety of foodstuffs and medications. Its major route of elimination from the body is in the urine. However, current knowledge concerning its glomerular filtration and, more particularly, its reabsorption/secretion is fragmentary. Most (80–90%) of Al in the plasma is normally bound to protein (mainly transferrin) and is therefore unfilterable; the remainder is bound to low molecular mass compounds, of which citrate appears to be the most important. In vitro determinations using artificial membranes indicate that ~10% of Al is filtered at normal plasma concentrations. However, when plasma Al is raised experimentally, its filterability falls, unless the excess Al is complexed with citrate; the aluminium citrate complex appears to be freely filtered. Information on tubular Al reabsorption at normal plasma concentrations is inconsistent. Filtered Al appears to be at least partially reabsorbed, although the reabsorptive mechanisms remain speculative. A consensus is emerging that elevated plasma Al concentrations result in a fall in fractional Al reabsorption, and a recent micropuncture study indicates that under these circumstances the only significant site of Al reabsorption is the loop of Henle.

Copyright © 2005 S. Karger AG, Basel

Introduction

Aluminium (Al), the most abundant metal in the Earth's crust, is present in a variety of foodstuffs (e.g. tea, self-raising flour) and medications (e.g. vaccines, antacids, phosphate binders) as well as in domestic water supplies. Although only a small fraction (normally ~0.2%) of ingested Al is absorbed into the blood [1], it is vital that absorbed Al is quickly removed from the body because Al accumulation is a risk factor in a number of disorders including microcytic anaemia, osteomalacia and dementia [2]. A small amount of Al is excreted in bile, but the major route of Al elimination is by the kidneys. Unsurprisingly, therefore, patients with renal insufficiency are more susceptible to Al toxicity [3]. Moreover, such patients often receive Al-based, phosphate-binding gels to control their serum phosphate, thereby exacerbating the problem. In addition, until the situation was recognised and largely rectified, many dialysis patients were exposed to increased risk owing to the high Al content of some dialysis fluids.

Given the key role of the kidneys in preventing harmful Al accumulation under normal circumstances, it is clear that strategies for dealing with cases of accidental exposure to high Al levels (as in the 'Camelford incident' in Cornwall, UK, in 1988, when aluminium sulphate was added to drinking water) need to focus on enhancing its renal elimination. Such strategies must rely on knowledge of the renal handling of Al (glomerular filtration, tubular reabsorption/secretion) and the factors that can affect these processes. Current knowledge is surprisingly fragmentary. In this minireview, we will attempt to piece together the available information on renal Al handling, at both physiological and pathological plasma concentrations.

Glomerular Filtration

Physiological Concentrations

A typical value for total body Al in a healthy subject is ~30 mg. A wide range of values has been reported for normal plasma Al concentration [see 4], probably because some early measurements were subject to contamination; more recent studies indicate a figure in the range 2–5 µg/l. Practically all Al in plasma exists as complexes, either with high molecular mass (HMM) or low molecular mass (LMM) compounds. As discussed in detail by van Landeghem et al. [4], attempts to quantify the various binding ligands have provided vastly differing results, depending on the methodologies used. A reasonable consensus is that 80–90% of Al is bound to protein, largely transferrin, whilst the remainder is bound to LMM compounds. The LMM anions in plasma that could potentially bind Al are citrate, phosphate, hydroxide and silicate. Of these, citrate is thought to be the principal, perhaps virtually exclusive, binder under normal circumstances [1, 4, 5].

It is reasonable to assume that Al bound to LMM compounds will be filtered at the glomerulus, whilst Al bound to HMM compounds will not. Direct assessment of glomerular filterability of Al in humans is obviously impossible, but indirect determinations have been made using artificial filtration membranes. Methodological errors associated with these have contributed to an enormous variety of reported values for 'ultrafilterable Al' (ranging from 6 to 95%), but a figure of around 10% has emerged from recent studies [4, 6], roughly in line with the proportion of Al bound to LMM compounds.

Even in animals, attempts to measure the filterability of Al at physiological plasma concentrations have relied on in vitro determinations using artificial membranes, since the volumes of glomerular filtrate that can be obtained by direct micropuncture collections in vivo are too small to allow measurement of such low Al concentrations. In the only study reported thus far (in rats), in vitro measurements indicated a surprisingly high figure of 60% filtration of endogenous Al [7], although the animals had received a considerable amount of saline and had been subjected to significant blood losses, thereby reducing plasma protein concentration and perhaps increasing the proportion of Al bound to LMM compounds.

Pathological Concentrations

Several studies have suggested that in patients with renal insufficiency, in whom plasma Al concentrations are often raised markedly, the ultrafilterable fraction of Al is slightly elevated [see 4], possibly owing to the raised

plasma phosphate concentrations (and therefore increased LMM binding) in these patients.

Induction of high plasma concentrations in rats has shown that filtration of Al is greatly dependent on both its concentration and speciation. When administered intravenously as aluminium chloride or aluminium sulphate, percentage filterability (measured in vitro) fell progressively as the plasma concentration increased [7, 8], whereas when aluminium citrate was infused, filterability was unaffected by plasma Al concentration, remaining at the relatively high value of ~80% [9]. In another study, using the same Amicon filtration system, but in which plasma Al was altered by addition of aluminium citrate to the drinking water, the subsequent intravenous infusion of citrate did not increase Al filterability [10]. The apparent contrast between these findings might reflect the differing protocols of the two studies. Two groups have measured Al filterability in vivo by collecting fluid directly from Bowman's space, made feasible by the use of Munich-Wistar rats whose kidneys have a number of surface glomeruli accessible to micropuncture. In order to allow the determination of Al concentrations in the small volumes of tubular fluid obtained, it was necessary to use very high doses of Al. In one, the Al was administered intravenously as aluminium chloride (plasma Al concentration ~25–120 × normal); Al filterability was inversely correlated to its plasma concentration, and ranged from 2 to 8% [11], echoing the in vitro findings of Lote et al. [7]. This low filterability at high concentrations is thought to be a consequence of formation of insoluble complexes [7]. More recently, a second micropuncture study has been performed using similar plasma concentrations, but with one important difference: the Al was administered as aluminium citrate [12]. In this case, filterability was found to be virtually 100% at each dose, which was significantly higher than the in vitro filterability measured simultaneously. To summarise: although important quantitative differences exist between in vitro and in vivo measurements, both approaches indicate that Al filterability is concentration dependent except when complexed with citrate.

Tubular Handling of Aluminium

In order to assess the tubular handling of Al, it is necessary to measure not only the glomerular filtration rate (GFR) and the renal clearance of Al (C_{Al}), but also its filterability. Studies in which all three variables have been determined are extremely rare.

Physiological Concentrations

Values for endogenous C_{Al} in healthy humans have been reported (or can be calculated from the published data) to be approximately 3 ml/min [13–15], equivalent to ~2% of the GFR (assessed by creatinine clearance) [14]. Recently, accelerator mass spectrometry has been employed to study the kinetics of tracer doses of orally administered ^{26}Al [6]. In 3 healthy males, C_{Al} averaged ~12 ml/min, equivalent to ~9% of the creatinine clearance. It is clearly impossible to arrive at a consensus figure for tubular Al handling from these disparate findings. Assuming that approximately 10% of plasma Al is filterable, fractional excretion of Al (FE_{Al}) would be between 20 and 90% of the filtered load.

In rats, Lote et al. [7] found that endogenous C_{Al} was ~8% of the simultaneously measured GFR, which accords with the findings of studies using ^{26}Al [16]. In contrast, data from another investigation in rats indicated a value for endogenous C_{Al} of ~20% of the GFR [10]. In the absence of information on the filterability of Al, it is not possible to determine how much, if any, Al was reabsorbed. Only Lote et al. [7] provided this information, and in that study there was evidence for substantial Al reabsorption in the nephron as a whole. No attempts to localise the nephron segments responsible have been possible, because the small volumes of tubular fluid obtained by micropuncture preclude the measurement of endogenous Al. Nor have any indirect approaches, such as treatment with selective diuretics, been applied. Possible mechanisms of Al reabsorption are by no means clear: as yet, no specific transporter systems for Al have been identified in renal tubular membranes. In mammalian brain, there is evidence that aluminium citrate can be carried on the H^+ -monocarboxylate transporter [17], and isoforms of this transporter are found in some nephron segments [18]; but it is not yet known whether renal isoforms can transport aluminium citrate. It might be supposed that at least some filtered Al would be reabsorbed passively in the proximal tubule, down its concentration gradient following water abstraction. However, a recent micropuncture study using high plasma concentrations of Al has shown that no significant passive Al reabsorption takes place in this segment (see below) [12].

Pathological Concentrations

Although information about altered tubular handling in uraemic patients with raised plasma Al concentrations is patchy, there is some indication that fractional Al reabsorption is reduced. C_{Al}/GFR (GFR being assessed as creatinine clearance) has been reported to increase in renal failure [14] and values in renal transplant patients under-

going immunosuppressive therapy are higher than those in healthy subjects [19, 20], but in no case was Al filterability measured. C_{Al}/GFR was also high (~30%) in a group of dialysis patients in whom creatinine clearance values were extremely low [21]. The ^{26}Al study of Steinhäuser et al. [6] indicated a modest increase in C_{Al}/GFR in renal failure patients, whilst a corresponding study in the 5/6 nephrectomy rat model [16] showed a more marked increase: 20% vs. 7% (although only 2 rats were studied).

In healthy animals, plasma Al concentrations have been artificially elevated by intravenous infusion; the consequences for Al excretion depend very much on the Al species used. Lote et al. [7] infused aluminium chloride and found that C_{Al} fell as the plasma concentration increased. The same observation was made in the isolated perfused rat kidney [22]. However, this is simply a reflection of the reduced filterability of Al at higher plasma Al concentrations. Lote et al. [7] showed that when filterability (measured *in vitro*) was taken into account, FE_{Al} increased markedly at the higher plasma Al concentrations. A similar conclusion was reached when intravenous infusions of aluminium citrate or aluminium sulphate were used: for both species of infused Al, FE_{Al} was ~70% at the highest filtered loads. Al excretion was much more efficient when citrate was infused (fig. 1), which was wholly attributable to the higher filterability of Al in this form [8].

In a pioneering study, Burnatowska-Hledin et al. [11] infused aluminium chloride into rats and calculated FE_{Al} by comparing the urinary excretion of Al with direct micropuncture measurement of ultrafiltered Al in glomerular filtrate. At plasma concentrations 25–120 × normal, FE_{Al} approximated 40%, which increased to >80% following volume expansion.

The first direct micropuncture assessment of segmental Al transport along the nephron has been performed recently in our laboratory. Using Munich-Wistar rats infused with three doses of aluminium citrate to achieve plasma concentrations of approximately 30, 60 and 120 × normal, Al deliveries to Bowman's space were compared with those at the end of the proximal convoluted tubule (PCT) and the beginning of the distal tubule, as well as in the final urine [12]. Somewhat surprisingly, at these high plasma concentrations and correspondingly high filtered loads, no evidence was found for significant net Al transport in the PCT. Owing to limitations in precision of measurement, the possibility of some Al reabsorption in the PCT cannot be discounted (which might be quantitatively significant at normal filtered loads), but it is clear that any such reabsorption must be subject to transport maximum limitation. In contrast to the PCT, we found that

Fig. 1. **a** Al excretion in the urine of rats following intravenous administration of bolus doses of Al as either sulphate or citrate. Values are means $\pm$ SEM. **b** Same experiment as figure 1a, but with Al excretion plotted against plasma Al concentration. Each point is a value from a single rat. **c** Same experiment as figure 1a, but with filtered load of Al (calculated as $GFR \times$ plasma Al concentration $\times$ Al filterability measured *in vitro*) plotted against plasma Al concentration. Each point is a value from a single rat. It is clear that the greater efficiency of Al excretion when administered as citrate is a consequence of the higher filtered load. Data taken from Lote et al. [8].

in all three groups a significant proportion of filtered Al (20–25%) was reabsorbed in the nephron segment between the late PCT and early distal tubule: the anatomical loop of Henle (fig. 2). In the absence of evidence for a specific Al transporter in the loop, we have speculated that the likely mechanism for Al reabsorption at this site is paracellular transport of free Al^{3+} ions in the thick ascending limb (TALH), driven by the lumen-positive

Fig. 2. Renal Al handling in rats infused with aluminium citrate at low dose (**a**), medium dose (**b**) or high dose (**c**), respectively raising plasma Al to concentrations 30, 60 and 120 $\times$ normal. Values are means $\pm$ SEM. F_{DAl} = Fractional delivery of Al to each puncture site, calculated by comparison with inulin deliveries; PCT = proximal convoluted tubule; NS = not statistically significant. Note that aluminium citrate is almost freely filtered into Bowman's space and that reabsorption in the PCT is statistically insignificant. Taken, with permission, from Shirley et al. [12].

transepithelial potential difference of this segment. Such transport would be analogous to that of Ca^{2+} and Mg^{2+} in the TALH, and it is worth noting that the effective ionic radius of Al^{3+} is less than that of either Ca^{2+} or Mg^{2+} .

The final observation of the micropuncture study was the absence of any evidence for net Al reabsorption beyond the loop of Henle at these high doses of Al [12]. However, at the highest dose, we did find evidence for some secretion of Al beyond the distal tubule. The mechanism of any such Al secretion is unknown, but our findings are consistent with earlier indirect evidence for Al secretion in the distal nephron of the pig [23].

In summary, although findings are not uniform between laboratories, there is some evidence that overall fractional reabsorption of Al within the nephron is significantly reduced at high plasma concentrations compared with that seen at normal endogenous plasma levels.

Conclusion

A considerable degree of confusion still exists with respect to the extent of Al filtration and reabsorption, particularly at normal plasma concentrations where mea-

surements are more difficult. However, it is possible to conclude from the literature that a substantial proportion of plasma Al is protein bound and therefore unfilterable, and that the filtration of elevated plasma Al concentrations is very much dependent on the nature of the anion species with which the excess Al is complexed. When the anion is citrate, it is clear that the balance of LMM/HMM binding is tilted so that Al is readily filtered. It is concluded, therefore, that in cases of Al toxicity an effective means of ridding the body of Al would be to raise plasma citrate concentrations; the enhanced filterability, together with only modest reabsorption along the nephron, would ensure a high rate of excretion. It should be noted, however, that since dietary citrate enhances Al uptake from the gastrointestinal tract [1], intravenous infusion of citrate would be the preferred route of administration.

Acknowledgement

Work in the authors' laboratories was supported by the National Kidney Research Fund, the Wellcome Trust, and the Medical Research Council.

References

- Yokel RA, McNamara PJ: Aluminium toxicokinetics: an updated minireview. *Pharmacol Toxicol* 2001;88:159–167.
- Hewitt CD, Savory J, Wills MR: Aspects of aluminum toxicity. *Clin Lab Med* 1990;10:403–422.
- Alfrey AC: Aluminum metabolism. *Kidney Int* 1986;29(suppl 18):S8–S11.
- Van Landeghem GF, de Broe ME, d'Haese PC: Al and Si: their speciation, distribution, and toxicity. *Clin Biochem* 1998;31:385–397.
- Öhman LO, Martin RB: Citrate as the main small molecule binding Al^{3+} in serum. *Clin Chem* 1994;40:598–601.
- Steinhausen C, Kislinger G, Winklhofer C, Beck E, Hohl C, Nolte E, Ittel TH, Alvarez-Brückmann MJL: Investigation of the aluminium biokinetics in humans: a ^{26}Al tracer study. *Food Chem Toxicol* 2004;42:363–371.
- Lote CJ, Wood JA, Saunders HC: Renal filtration, reabsorption and excretion of aluminium in the rat. *Clin Sci* 1992;82:13–18.
- Lote CJ, Wood JA, Thewles A, Freeman M: Renal filtration and excretion of aluminium in the rat: dose-response relationships and effects of aluminium speciation. *Hum Exp Toxicol* 1995;14:494–499.
- Lote CJ, Saunders HC, Wood JA, Spencer AJ: Effect of citrate on plasma aluminium concentration and aluminium excretion in the rat. *Clin Sci* 1992;83:431–435.
- Cochran M, Chawtur V, Phillips JW, Dilella B: Effect of citrate infusion on urinary aluminium excretion in the rat. *Clin Sci* 1994;86:223–226.
- Burnatowska-Hledin MA, Mayor GH, Lau K: Renal handling of aluminum in the rat: clearance and micropuncture studies. *Am J Physiol* 1985;249:F192–F197.
- Shirley DG, Walter MF, Walter SJ, Thewles A, Lote CJ: Renal aluminium handling in the rat: a micropuncture assessment. *Clin Sci* 2004;107:159–165.
- Wilhelm M, Höhr D, Abel J, Ohnesorge FK: Renal aluminum excretion. *Biol Trace Elem Res* 1989;21:241–245.
- Burgess E, Muruve D, Audette R: Aluminum absorption and excretion following sucralose therapy in chronic renal insufficiency. *Am J Med* 1992;92:471–475.
- Chiba J, Kusumoto M, Shirai S, Ikawa K, Sakamoto S: The influence of fluoride ingestion on urinary aluminum excretion in humans. *Tohoku J Exp Med* 2002;196:139–149.
- Meirav O, Sutton RAL, Fink D, Middleton R, Klein J, Walker VR, Halabe A, Vetterli D, Johnson RR: Accelerator mass spectrometry: application to study of aluminum kinetics in the rat. *Am J Physiol* 1991;260:F466–F469.
- Ackley DC, Yokel RA: Aluminum transport out of brain extracellular fluid is proton dependent and inhibited by mersalyl acid, suggesting mediation by the monocarboxylate transporter (MCT1). *Toxicology* 1998;127:59–67.
- Garcia CK, Brown MS, Pathak RK, Goldstein JL: cDNA cloning of MCT2, a second monocarboxylate transporter expressed in different cells than MCT1. *J Biol Chem* 1995;270:1843–1849.
- Davenport A, Davison AM, Newton KE, Will EJ, Giles GR, Toothill C: Urinary aluminium excretion following renal transplantation and the effect of pulse steroid therapy. *Ann Clin Biochem* 1990;27:25–32.
- Grosso S, Douthat W, Garay G, de Arteaga J, Boccardo G, Fernández Martín JL, Canteros A, Cannata Andía J, Massari P: Time course and functional correlates of post-transplant aluminium elimination. *Nephrol Dial Transplant* 1998;13(suppl 3):98–102.
- Altman P, Butter KC, Plowman D, de Saintonge DMC, Cunningham J, Marsh FP: Residual renal function in hemodialysis patients may protect against hyperaluminemia. *Kidney Int* 1987;32:710–713.
- Höhr D, Abel J, Wilhelm M: Renal clearance of aluminium: studies in the isolated perfused rat kidney. *Toxicol Lett* 1989;45:165–174.
- Monteagudo FSE, Isaacson LC, Wilson G, Hickman R, Folb PI: Aluminium excretion by the distal tubule of the pig kidney. *Nephron* 1988;49:245–250.