Aluminium contamination in products for parenteral nutrition

1. Introduction

In the 1970s, aluminium (Al) toxicity was first implicated in the bone disease and neurologic complications seen in patients receiving chronic haemodialysis (Ward 1978). It could be shown that toxicity occurred after water was used for preparation of dialysis solutions that was highly contaminated with Al. Since the 1980s, Al contamination of parenteral nutrition (PN) has also been recognised as a problem (Klein 1980; Sedman 1985). At that time, the daily Al intake from PN was estimated to be 50-100 times greater than the current estimated intake. The high concentrations found a quarter of a century ago mainly came from casein hydrolysates, which were used as a protein source for PN and are rich in Al. They have now been completely replaced by crystalline amino acids that have a much lower overall Al load (Klein 1982, Gura 2006).

However, Al toxicity continues to concern healthcare professionals who are involved in the production, prescription and administration of PN. Recent publications, such as the A.S.P.E.N. Statement on Aluminium in Parenteral Nutrition Solutions (A.S.P.E.N. 2004), that of Driscoll et al. (2005), who analysed the Al contamination especially of small volume parenterals, and a review by Gura & Puder who in 2006 evaluated recent developments concerning Al contamination of PN products (Gura 2006), provide an update of the available information.

This document briefly reviews the issues associated with sources of Al contamination in PN formulations, possible effects of high Al intake, parenterally fed patients groups at high risk, efforts undertaken to reduce Al contamination in PN formulations, and available data concerning Al contamination of Fresenius Kabi (FK) products for PN.

2. Origin of contamination and exposure to aluminium

Aluminium is the third most common element in the earth's crust (believed to be 7.5% to 8.1%) and one of the most abundant metals in the environment. It is usually found in the ionic form, a trivalent cation, and is present in this form in most animal and plant tissues. However, Al is one of the few abundant elements that appear to have no biological function.

Humans are exposed to Al via a huge number of sources, among them water, food, cooking utensils, dust particles, cosmetics, and medicinal products. It is estimated that humans ingest 5 to 20 mg of Al per day, but the amounts can be considerably higher when aluminium utensils are used for cooking. However, the gastrointestinal tract is an effective barrier to Al absorption as a consequence of the limited solubility of Al and the restricted permeability of intestinal mucosa to aluminium. Typically, gastrointestinal absorption of aluminium from diets is < 1%. Also skin and lungs are effective barriers to Al absorption. Once absorbed, the main route of elimination is by the kidneys (Greger 1997, Soni 2001).

Intravenously administered Al bypasses the protective barrier of the gastrointestinal tract. Thus, particularly in patients with impaired or immature renal function, contamination of parenteral medications can lead to Al accumulation in the body.

3. Toxicity of aluminium

No reports of dietary Al toxicity to healthy individuals exist in the literature. There is evidence of toxicity of Al in some tissues, mainly in bone and brain. Accumulation in the brain seems to have neurotoxic effects. Cognitive and other neurological deficits were reported among groups of workers occupationally exposed to dust containing high levels of Al (Soni 2001). Aluminium is suspected to adversely affect bone *formation*. Moreover, studies both in vivo and in vitro provided evidence that Al may also impair bone *mineralisation*. Aluminium may cause anaemia through decreased heme synthesis and other effects on blood components, and in recent years, Al has been implicated in the development of Alzheimer disease.

Aluminium can especially accumulate in patients with impaired renal function and in newborns (Ganrot 1986, Gruskin 1988). Beside the complications reported after use of highly Al contaminated water for dialysis solutions, (Ward 1978) progressive encephalopathy has been observed in renally impaired children after having received large amounts of Al-containing phosphate binders over months (Gruskin 1988). Bone disease, but not encephalopathy, was identified in adult patients with normal renal function who were receiving long-term parenteral nutrition (Klein 1980). In the mid- 1980s, Al loading was found in the serum, urine and bones of preterm infants after 3 weeks of total parenteral nutrition (TPN) (Sedman 1985), and it was detected that Al accumulated in the mineralisation front of bones of premature infants (Koo 1986). All these findings in connection to PN originate from the 1970s and 1980s, when highly contaminated protein hydrolysates were administered as protein components.

No further evidence of Al toxicity in preterm infants was reported until 1997, when Bishop et al. (Bishop 1997) showed impaired mental development in 18-month old infants, who as preterm babies had received TPN containing 45 µg Al/kg/d, compared to a group who had received Al-reduced TPN with 4 to 5 µg Al/kg/d. Al reduction was achieved by replacing calcium gluconate with calcium chloride and potassium acid phosphate with a mixed sodium-potassium phosphate.
A significant difference ($p=0.02$) in the Bayley Mental Development Index was only found in a subgroup in whom the duration of parenteral feeding exceeded the median of 10 days, and who did not have impaired neuromotor development. This subgroup consisted of 39 out of 90 infants who received the standard formulation and 41 out of 92 infants who received the Al-reduced formulation.

The biochemical basis of Al toxicity is not completely understood. Due to its atomic size and charge, is can be a competitive inhibitor of other elements such as calcium, magnesium, and iron. However, toxic intake levels of Al could not be established. Also a "safe" lower limit could not be proved.
Nevertheless, based solely on the above mentioned study of Bishop et al., the US FDA established that up to **4-5 µg/kg/day of Al taken parenterally is safe** (FDA 2000).

Furthermore, they established a limit for Al contamination in products for PN (see below). Methodological flaws of the Bishop study led to discussion of the limitations of the FDA mandate (Gura 2006, Canada 2005).

There are still controversies about the causal relationship of the reported complications with Al accumulation. Furthermore, the diagnosis of Al toxicity is difficult due to the lack of standardised testing. Evaluation of clinical signs and symptoms in conjunction with laboratory tests are recommended, including mental status changes, bone pain, proximal muscle weakness, multiple nonhealing fractures or premature osteoporosis. Plasma levels of Al are thought to be a poor predictor of the presence or absence of toxicity (Gura 2006).

4. Aluminium contamination through medicinal products

Oral antacids:
Important Al sources are antacids with daily doses of up to approx. 1 g Al/day. Therefore such products are contraindicated or should only be used with caution in patients with *significant renal impairment* (in mild renal impairment even these products seem to be safe).

Dialysis solutions:
Once safe standards were established for Al concentration in dialysis solutions, the incidence of Al toxicities, including dialysis encephalopathy and osteomalacia, reduced dramatically (Sedman 1985).
After a Resolution of the European Community (EC 1986), the Al content of dialysis fluids was monitored and reduced. In the EC, the concentration of Al in haemofiltration solutions must not exceed 10 mg/L and the level of Al in the diluted solution for haemodialysis must not exceed 30 mg/L.
This upper limit for Al concentration in haemodialysis solutions has been proved safe over the last 20 years.

Parenteral nutrition solutions:
The high Al concentrations of TPN in the 1970s and 1980s mainly came from casein hydrolysates, which have completely been replaced by crystalline amino acids. Amino acid solutions now have a much lower overall Al content (Gura 2006).
However, the concentration of Al in TPN solutions is highly variable (Recknagel 1994, Bohrer 2002, Driscoll 2005). Large Volume Parenterals (LVPs, > 100 ml) in general are less contaminated than Small Volume Parenterals (SVPs, ≤ 100 ml), with additives containing calcium and inorganic phosphate salts being the chief sources of contamination.

In 1994, from long-term PN in Germany, a daily Al load of 3.5±0.4 µg/kg b.w. in children and of 2.2±1.8 µg/kg b.w. in adults was reported. 59±6 % of the intravenous Al load in children and 42±16 % in adults was due to the highly contaminated small-volume calcium, inorganic phosphate, trace element and vitamin additives (Gramm 1994).

In the USA, after long years of discussion, in 2000 the FDA (FDA 2000) defined that the Al content in LVPs must not exceed 25 µg/L. This rule applies to, but is not limited to, parenteral amino acid solutions, glucose solutions, lipid emulsions, and sterile water for injection. For

SVPs no limit was set, but labelling of the maximum Al content at expiry is now required. The concentration of Al in SVPs is often by far higher than in LVPs. This rule applies to, but is not limited to, electrolyte solutions, multivitamin solutions, and trace elements. All LVPs and SVPs must include a warning in the prescribing information that reads as follows:
"WARNING: this product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day, accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration."
The final effective date of the rule was July 2004.

To date, for LVPs and SVPs in the European Union or elsewhere outside the USA, no such rule has been implemented and no labelling of the Al content or corresponding warning is required.

Other parenterals

Other intravenous products which are frequently infused in patients requiring PN often contain considerable amounts of aluminium, among these are albumin and heparin (Wilhelm 2001, Klein 1995). Contamination of albumin products was shown to be mainly caused by industrial processing of human albumin (Klein 1995).
Concerning albumin products, Canada, some European countries, China, and many other countries now require Al content to be less than 200 µg/L.

5. Sources of aluminium contamination in parenteral nutrition solutions

Glass containers:

Of all sources of Al contamination of parenterals, glass is the most important one (Baumann 1998). The quality of the glass and the surface/volume ratio (particularly for glass ampoules) strongly influence the Al contamination of the finished product. The glass of ampoules (hard glass - type I USP) contains approx. 6% Al, whereas usually the glass of bottles (soft glass - type II/III USP) contains about 2% Al (Wurdack 2006). The migration of Al from glass is influenced by the components of the solution it contains, its pH value and the corrosiveness.
In different electrolyte additives, up to 90% of the Al contamination after sterilisation originated from the glass container. This could be shown when the same salt solutions were filled in glass bottles (type II) and in polyethylen bottles (Baumann 1998).
Bohrer et al. (Bohrer 2001 and 2003) have shown that solutions stored in plastic containers elute almost no Al, whereas in glass the Al contamination can reach 1,000 µg/L and more, and that the Al content increases with storage time. During the sterilisation process, even pure water was able to extract Al from glass. The Al released from glass ampoules was between 20 µg/L for non-critical solutions and 1500 µg/L for solutions of basic phosphates and bicarbonate.

Recent investigations by Wurdack (2006) confirm that the elution of Al ions from glass containers is increased for small glass containers such as ampoules or vials in comparison to larger ones, i.e. bottles.

Raw materials:
Some raw materials contain significant amounts of Al. Among such raw materials used in PN are calcium and phosphate salts and vitamins (Koo 1986, Recknagel 1994).
Examples of PN raw materials with only low Al concentrations are amino acids, lipids and glucose. Lipids seem to be least contaminated.

6. Conclusions

The evidence on which the FDA regulations are besed on regarding the Al content of Large and Small Volume Parenterals is very weak. This could be the reason why up to now other countries have not established similar rules. However, among experts it is agreed that Al contamination in intravenous products should be as low as possible and that at least the most vulnerable group, pre-term and newborn infants, must be protected from an excessive intravenous Al load whenever possible. Manufacturers of products for PN are aware of their responsibility and have taken measures to keep the Al contents of their products as low as possible. However, for the time being, parenteral feeding cannot be offered totally free of Al, mainly because of the unavoidable contamination of the necessary electrolytes and vitamins and, to a lesser degree, other nutrients. Pharmacists can reduce the Al content of PN admixtures if they use products packed in plastic rather than in glass whenever possible.

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