Aluminum exposure and toxicity in neonates: a practical guide to halt aluminum overload in the prenatal and perinatal periods

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Background: **During the last years, human newborns have been overexposed to biologically reactive aluminum, with possible relevant consequences on their future health and on their susceptibility to a variety of diseases. Children, newborns and particularly preterm neonates are at an increased risk of aluminum toxicity because of their relative immaturity.**

Data sources: **Based on recent original publications and classical data of the literatures, we reviewed the aluminum content in mother's food during the intrauterine life as well as in breast milk and infant formula during lactation. We also determined the possible role of aluminum in parenteral nutrition solutions, in adjuvants of vaccines and in pharmaceutical products. A special focus is placed on the relationship between aluminum overexposure and the insurgence of bone diseases.**

Results: **Practical points of management and prevention are suggested. Aluminum sources that infants may receive during the first 6 months of life are presented. In the context of prevention of possible adverse effects of aluminum overload in fetal tissues during development, simple suggestions to pregnant women are described. Finally, practical points of management and prevention are suggested.**

Conclusions: **Pediatricians and neonatologists must be more concerned about aluminum content in all products our newborns are exposed to, starting from monitoring aluminum concentrations in milk- and soy-based formulas in which, on the basis of recent studies, there is still too much aluminum.**

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Review article

Introduction

Human newborns are experiencing a massive exposure to biologically reactive aluminum, with possible relevant consequences on their future health and susceptibility to a variety of disease states.[1] Although it is not absolutely well established that aluminum causes adverse effects on human health, children, newborns and particularly preterm neonates are at an increased risk of aluminum toxicity because of anatomic, physiologic and nutrition-related factors not present in other populations.[2] Preterm infants have recently been included among the four groups of people at elevated risk of systemic aluminum intoxication after repeated ingestion of monomeric aluminum salts.[3] Aluminum overload has been demonstrated in neonates, particularly in premature infants undergoing parenteral nutrition or receiving intravenous fluid therapy.[4] Premature neonates requiring high doses of calcium and phosphate for bone mineralization, children with impaired renal function and children on parenteral nutrition therapy for prolonged duration are generally considered at the highest risk for aluminum toxicity.[5] In 2004, the Food and Drug Administration (FDA) recommended restricting daily aluminum

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administration to 5 μg/kg per day and now requires that additives used to compound parenteral nutrition have the maximum aluminum content at expiration listed on the product label.[6] But, what is the real risk of aluminum overexposure in the general neonatal population? What consequences in childhood and in adulthood may be expected in newborns undergoing aluminum overload in the perinatal period?

Here, we will review the recent data on the risk of aluminum exposure for the health of neonates, in particular, for the possible severe consequences on the brain and bone metabolism in childhood and adulthood.

Aluminum in mother's food during the intrauterine life

The effects of oral aluminum on the metabolism of essential trace elements, including calcium, magnesium, manganese, copper, zinc and iron, have been studied in rats during pregnancy. In the aluminum-treated pregnant animals, the higher levels of the metal were detected in the liver. With regard to the essential trace elements, oral aluminum exposure during pregnancy produced significant changes in tissue distribution of a number of essential trace elements: copper concentrations in the brain were significantly higher, as well as the calcium levels in bone, whereas renal concentrations of calcium, magnesium, manganese, copper, zinc and iron were significantly increased. Taken together, these experimental data suggest that oral exposure during pregnancy can produce significant changes in the tissue distribution of multiple essential trace elements, with possible consequences on fetal metabolism.[7] Oral exposure to aluminum-containing products, including antacids which represent the most important source of human aluminum overexposure, has recently been proposed as a possible cause of embryonic and fetal toxic effects.[8] To prevent possible adverse effects on fetal development, the use of aluminum-based antacids should be limited during pregnancy, in particular when concomitantly assumed with citrate-containing beverages which significantly increase the absorption of aluminum ions in the gut.[8] Moreover, the presence in the diet of chelating agents such as citric acid, found in large amounts in fruit, has been shown to enhance aluminum absorption.[9] The risk of aluminum overload has been reported in subjects taking an analgesic/antipyretic with a high aluminum content.[10] These data indicate that caution should be taken with common anti-reflux medications such as antacids that contain aluminum and other aluminum-containing drugs during pregnancy to protect the newborn from a possibly dangerous aluminum overload during gestation.

Aluminum in breast milk and infant formulas

Aluminum is normally present in human breast milk, and its content ranges from 15 μg/L to 30 μg/L, which is between 10 and 40 times lower than the aluminum concentration in infant formulas.[11] Many infant formulas are cow's milk-based feeds for infants developed as alternatives to breast milk and designed to meet the specific nutritional needs of preterm babies, low birth weight neonates, at term newborns through to infants of several years of age.[12] To meet the needs of neonates with intolerances to cow's milk components, soy protein-based formulas have been developed in recent years.[13] More than 25 years ago, aluminum intoxication was described in newborns fed with infant formulas, as the consequence of the presence of aluminum as a contaminant.[14,15] In fact, contrasting with the low aluminum content normally found in human milk, ranging from 4 μg/L up to 65 μg/L, the metal content in premature infant formulas has been reported to range from 100 μg/L up to 900 μg/L.[16] In the following years, several reports[10,17-20] demonstrated the presence of high levels of aluminum in the vast majority of available infant formulas, thus highlighting the urgent need to reduce the aluminum content of infant formulas to lower levels in the context of prevention of possible toxic effects of the metal ions in childhood and adulthood. A recent study[21] focused on aluminum concentration in 15 different branded infant formula products. The metal content ranged from 176 μg/L up to 700 μg/L, and the soy-based products showed the highest aluminum concentrations. According to these data, the average daily ingestion of aluminum for children on infant formulas has been estimated to range from 206 μg/L up to 592 μg/L per day. Consequently, the average ingestion of aluminum during the first six months of life for children on cow's or soy formulas may be estimated to range from 37 mg up to 106 mg, respectively.

The presence of too much aluminum in infant formulas and in particular in soy-based formulas has been confirmed.[22] The high aluminum content in the soybean plant which, on growing in acid soils, comes into contact with aluminum ions. These ions, in an acidic environment, may dissociate from aluminum-silicates and become absorbable by soybean roots.[23] The possible explanation for high aluminum content in many infant formulas may be more complex: the sources of such contamination include the use of aluminum-based materials for their packaging or contamination of the single constituents of the formulas.[24]

Aluminum in parenteral nutrition solutions

Preterm infants have been found to be at risk of

aluminum overload when submitted to prolonged intravenous feeding and develop neurotoxicity which may be present in childhood or later in life with a mental development index of less than 85 and subsequent educational problems.[25] The contamination of parenteral solutions with aluminum salts has been reported as one of the main factors responsible for the development of metabolic bone disease in parenteral nutrition patients, particularly in preterm newborns, leading to osteopenic bone disease.[26] Elevated concentrations of aluminum have been reported in infants receiving intravenous therapy[27] and in children undergoing protracted regimens of parenteral nutrition, caused by parenteral drug products containing aluminum as an ingredient.[28]

Aluminum exposure in the perinatal period has been hypothesized as having a strong impact on the health status in childhood and adulthood, sometimes even when aluminum overexposure is restricted to a short period. It has been demonstrated that when parenterally fed, neonates may retain up to 78% of the aluminum administered, with high aluminum serum, urine and tissue levels. To better understand the possible consequences on human health of aluminum overexposure in neonates, a recent randomized trial compared standard parenteral nutrition solutions with solutions specifically sourced for low aluminum content. Preterm neonates exposed for more than 10 days to standard solutions had impaired neurologic development at 18 months, as compared to infants receiving solutions specifically sourced for low aluminum content. Moreover, at 13-15 years, the same subjects randomized to standard parenteral nutrition had a bone mass at the lower lumbar spine, a finding indicative of significant modifications of bone metabolism, putatively induced by exposure to high aluminum levels in the perinatal period.[29]

Aluminum as an adjuvant in pediatric vaccines

Aluminum can be found in multiple childhood vaccines, including hepatitis B, polio, hepatitis A, haemophilus influenzae type B, diphtheria, tetanus and pertussis (DPT), human papilloma virus (HPV) and pneumococcal vaccines.[30] Aluminum plays a vital role in enabling the basic vaccines to be used effectively, and non-aluminum adjuvants may readily replace aluminum.[31] The fundamental role of aluminum in increasing the bioavailability of antitetanus vaccine has recently been described. Shaking of the product during transport has been shown to lead to collapse of the gel matrix of aluminum hydroxide, resulting in desorption of the tetanus toxoid from the matrix, which then loses its antigenicity. The incorporation of sorbitol, glucose and arginine has been demonstrated to protect the adjuvant matrix, thus retaining the integrity of the vaccine preparation in terms of its antigenicity.[32]

Although it has been claimed that immunization with aluminum-containing vaccines is associated with adverse effects in children, a systematic review with meta-analysis has clearly shown that there is no evidence that aluminum salts in vaccines cause any serious or long-lasting adverse events. Jefferson et al[33] found that vaccines with aluminum hydroxide against DPT caused significantly more erythema and induration than plain vaccines, particularly in young children. In older children, an association with local pain lasting up to 14 days was also reported.[33]

Aluminum in pharmaceutical products

Full-term and particularly preterm neonates are susceptible to accumulation of aluminum ions in tissues while receiving parenteral nutrition, as demonstrated by high aluminum levels detected in brain and bone samples.[34] An experimental study[35] has also shown that parenteral aluminum administration may be responsible for hepatotoxicity. Another study[36] in premature infants undergoing parenteral nutrition showed a relationship between the degree of aluminum contamination of the parenteral nutrition solutions and the degree and severity of cholestasis. Recent data on aluminum content in routinely used parenteral nutrition solutions evidenced concentrations of the metal meeting or exceeding the FDA threshold for aluminum in all the solutions utilized for treating neonates.[37] These data indicate that the problem of aluminum overexposure in neonates is still an unsolved problem in clinical practice. A 15-year follow-up of a cohort of 59 preterm infants who were exposed to aluminum from parenteral nutrition solutions in the perinatal period showed a reduced lumbar spine and a hip bone mass during adolescence, a potential risk factor for osteoporosis and hip fractures.[38]

Aluminum exposure in the perinatal period and bone disease

Preterm infants are at risk of metabolic bone disease (MBD) because of an inadequate mineral intake, clinical rickets and fractures being common in this population.[39] Although infants with MBD are frequently asymptomatic in the perinatal period, the hypothesis that early nutrition programs affect later bone health and peak bone mass is generally accepted, and MBD in the perinatal period can predict reduced

linear growth in infancy and childhood.[40] A 20-year follow-up of 202 subjects who were born preterm and randomized to early diet clearly showed that breast feeding was associated with a higher whole body bone mass, with possible important implications for later osteoporosis risk.[41]

The toxic effects of aluminum overload on bone metabolism were first reported, or better hypothesized, in 1978, in an article describing a severe form of osteomalacic osteodystrophy occurring in patients undergoing dialysis.[42] Six years later, severe osteomalacia associated with massive aluminum deposition in bones was reported in three infants not undergoing dialysis but subjected to treatment with aluminum hydroxide as a phosphate binder.[43] Further studies demonstrated a close correlation between treatment with aluminum hydroxide and increase of serum aluminum levels,[44,45] followed by increased aluminum concentrations in bone.[46] The association between aluminum overload and bone disorders has been confirmed by several case reports. Fractures, osteopenia and osteomalacia, caused by aluminum deposition in the zone of provisional calcification and along the newly formed bone trabeculae, have been found in infants who received aluminum-containing antacids.[47] Adverse effects of aluminum-contaminating parenteral nutrition solutions on bone formation in infants, and particularly in preterm infants, regarding the development of osteopenic bone disease, have been described.[25] Infants and children with immature or impaired renal function are considered at higher risk of developing aluminum-related osteomalacia.[48]

But how can aluminum overload cause bone metabolism disarrangement leading to osteomalacia? First of all, it should be taken into account that, once absorbed, aluminum ions accumulate in the brain, liver, kidney and bone, with bone as the major site for aluminum deposition in humans.[41] It has been shown that plasma aluminum levels above 100 μg/L represent a risk factor for aluminum bone toxicity.[49] A recent study carried out on young growing rats regarding the toxic effects of overexposure to aluminum on bone formation evidenced a higher accumulation of the metal in bones of treated animals.[50] In that study, a disordered metabolism of calcium and phosphorus was found in rats undergoing overexposure to aluminum, when compared with control rats. The levels of parathyroid hormone, calcitonin, osteocalcin, procollagen carboxy-terminal propeptide and bone alkaline phosphatase were significantly lower in aluminum-treated rats, and the bone mineral density of femoral metaphysis was significantly lower, clearly suggesting that aluminum exposure inhibits bone formation and induces bone loss.[50] A possible influence of aluminum overload on bone formation during embryogenesis has been highlighted by multiple studies carried out in chick embryos. Aluminum administration resulted in malformations of tibias and femurs, associated with a bone mineralization defect: tibias from chick embryos that were administered aluminum salts contained significantly less bone calcium compared with tibias from control embryos.[51] Regarding the intimate action of aluminum ions on bone metabolism, the results of the experimental animal studies are consistent with a direct adverse effect of this metal on osteogenesis, resulting in major changes in calcium influx and afflux from bone, suppression of new bone formation and in the increase of calcium mobilization from bone.[52] Aluminum exposure has been hypothesized to impair the synthesis of new bone matrix, and this response of bone may be mediated through a toxic effect of aluminum ions on bone cells responsible for the deposition of new osseous matrix, the osteoblasts.[53] A specific action of aluminum to inhibit the mineralization of bone *in vivo* leading to osteomalacia has not yet been demonstrated. The role of parathyroid hormone in the pathogenesis of the osteomalacia that develops after aluminum overloading also remains uncertain.[54] It has been hypothesized that hyperparathyroidism is at least initially involved in the pathogenesis of osteomalacia.[55] Aluminum has been shown to be toxic to osteoblasts and also to directly inhibit mineralization even when osteoblasts are not decreased. Moreover, aluminum administration was able to block mineralization of osteoid, with persistent osteomalacia.[56] A paradoxical toxic and trophic action of aluminum ions has been reported on osteoblasts, both in animal models and in "culture" systems. In osteoblast cell lines, aluminum is mitogenic in some and shows anti-proliferative activity in others. The speciation of aluminum ions may contribute to its differential action on bone forming cells, resulting in paradoxical toxic and trophic effects.[56]

Rats given drinking water containing aluminum chloride showed lower bone deposition of calcium, phosphorus and magnesium when compared with control rats, associated with a significantly lower bone mineral density of femur metaphysis, indicating that aluminum exposure reduces the levels of mineral trace elements in bone.[57-59]

Conclusions

Our newborns are experiencing too high levels of absorbable aluminum during intrauterine life and in the perinatal period. This fact raises many questions regarding their present and future health in childhood and adulthood. Although it is not completely established

Table. Aluminum sources that infants may receive during the first 6 months of life[1,11,61,62]

Sources	Amount
Breast milk	10 mg
Infant formula	40 mg
Soy-based formula	120 mg
Vaccines	4 mg
Parenteral nutrition	16.67 mmol/L*
Antiacids	Unknown

*: mean daily assumption.

that aluminum exposure always causes adverse effects on human health, epidemiological and experimental data suggest that the introduction of high quantities of aluminum to tissues such as the brain and bone leads to structural modifications of many cell constituents, with major changes in calcium metabolism, aluminum ions being able to compete with and displace calcium ions from proteins. Moreover, the ability of aluminum ions to increase the production of reactive oxygen species by transition metal ions, including iron and copper, may represent a link between aluminum overload and oxidative stress, inducing apoptotic cell death in many organs and systems. The increasing number of reports in recent years regarding overexposure of newborns to aluminum probably indicates that what we have experienced over the past years may represent the tip of an iceberg. Taken all together, these findings should lead neonatologists to be much more concerned about aluminum content in all products our newborns are exposed to, starting from monitoring aluminum concentrations in milk- and soy-based formulas in which, on the basis of recent studies, there is still too much aluminum (Table).[11,60,61]

Taking stock of the situation reported here regarding our knowledge on aluminum exposure of neonates, the following critical points may be summarized, in the context of the prevention of possible adverse effects later in life related to aluminum overexposure in the perinatal period: 1) Human embryos and fetuses are at higher risk of developing aluminum storage, particularly in the developing osseous and nervous tissues; 2) Preterm neonates are at risk of aluminum overload, given the immaturity of the intestinal barrier, which represents the most important filter for aluminum absorption, the rapid uptake of aluminum ions by developing tissues and the immaturity of kidneys, the most important tools for aluminum excretion; 3) Preterm and term newborns undergoing parenteral nutrition and/or intravenous therapy are at risk of aluminum intoxication, given the contamination of parenteral solutions with aluminum and its direct introduction into their blood, thus bypassing the intestinal barrier, and 4) Neonates affected by renal disease are at risk of aluminum storage due to their decreased ability to excrete metal ions and to the frequent use of antacids in this population.

In the context of prevention of possible adverse effects of aluminum overload in fetal tissues during development, simple suggestions to pregnant women are as follows: 1) Avoid drinking acidic beverages or tea in aluminum cans; 2) Restrict tea assumption, avoid adding lemon which increases aluminum absorption from tea, and encourage the addition of milk, which lowers the pH of tea infusions and decreases aluminum bioavailability; 3) Limit the use of aluminum-containing antiperspirants or toothpastes; 4) Avoid assumption of coffee beverages obtained using aluminum mokas, given the massive aluminum leakage during coffee solution preparation; 5) Limit consumption of food cooked in aluminum pots, as well as food stored and packaged in aluminum containers; 6) Limit eating of cheese or cakes containing aluminum; 7) Restrict the use of herbal products in which the level of contamination of aluminum is not indicated; 8) Avoid, during lactation, the use of aluminum-based beauty products and antiperspirants; 9) Choose drinking water utilized for formulas among those with a low aluminum content; 10) Test aluminum content both in powdered and ready-made liquid formulas, favoring those with the lowest levels of aluminum contamination, according to nutritional requirements; 11) Always test aluminum content in soy-based formulas, whose prolonged use may lead to a significant increase in aluminum body burden, with possible relevant clinical consequences in childhood; 12) Accurately check aluminum content in solutions utilized for parenteral nutrition, particularly in preterm neonates, whose aluminum renal excretion should be accurately verified to obtain useful information on the amount of aluminum stored in different organs; 13) Avoid the use of aluminum-containing drugs, including antacids, in newborns receiving parenteral nutrition and in neonates affected by renal insufficiency; 14) Do not delay aluminum-containing vaccines, due to the relatively small amount of aluminum contained in pediatric vaccines.

In conclusion, it is clear that aluminum represents a significant component of newborns' exposure to xenobiotics and contaminants, that preterm infants are at a high risk of aluminum overload with possible pathological consequences, not only in the perinatal period, but even in childhood and adulthood. An ambitious but measured plan aimed at preventing aluminum overexposure in neonates should be initiated by the community of gynecologists and neonatologists, starting with the following options: alerting the medical community about the risk of aluminum exposure in the early period of life; and extending with caution information to pregnant women and to mothers

about the vulnerability of infants to early exposure to this metal ion, eventually forcing manufacturers to indicate the level of aluminum contamination in every neonatal product. Such a plan may put perinatologists at the center of a new challenge: to reduce aluminum-related human pathology, not only in neonates but even in children and adults, probably participating in the prevention of the epidemic increase of neurodegenerative diseases of elderly people.[1,62]

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