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Aluminum Contamination in Parenteral Nutrition Admixtures for Low-Birth-Weight Preterm Infants in Mexico

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Abstract

Background: Aluminum contamination from intravenous solutions still represents an unsolved clinical and biochemical problem. Increased aluminum intake constitutes a risk factor for the development to metabolic bone disease, anemia, cholestasis, and neurocognitive alterations. Low-birth-weight preterm infants (LBWPIs) are one of the most exposed populations for aluminum toxicity. *Methods*: To determine the presence of aluminum in components employed in the preparation of parenteral nutrition (PN) admixtures in Mexico and compare with the maximal aluminum recommended intake from the Food and Drug Administration. *Results*: Cysteine, trace elements, levocarnitine, phosphate, and calcium salts tested positive for aluminum contamination. All components analyzed were contained in glass vials. Total aluminum intake for 2 sample PN admixtures were calculated in basis to cover nutrition requirements of 2 hypothetical LBWPIs. Aluminum contents, stratified in micrograms per kilogram of weight, exceeded maximal aluminum recommendations, particularly for the very LBWPIs. Substituting sodium phosphate for potassium phosphate salts reduced aluminum intake by 52.7%. Calcium gluconate was the leading aluminum contamination source and confers the greatest risk for aluminum overdose, even with the salt substitution of potassium phosphate by sodium phosphate salts. Adding cysteine and trace elements might increase aluminum content in PN admixtures. *Conclusion*: Cysteine, trace elements, phosphate, and gluconate salts are the main sources of aluminum in PN prepared in Mexico. Substituting sodium phosphate for potassium phosphate salts reduces aluminum intake but does not resolve aluminum contamination risk. Mineral salts contained in plastic vials should be explored as an additional measure to reduce aluminum contamination. (*JPEN J Parenter Enteral Nutr*. 2016;40:1014-1020)

Keywords

aluminum; toxicity; metabolic bone disease; osteomalacia; low-birth-weight preterm infants; parenteral nutrition

Clinical Relevancy Statement

Excessive aluminum intakes from intravenous solutions, drugs, and parenteral nutrition still represent an unsolved problem. Potential toxicities and side effects have been widely described. Low-birth-weight preterm infants, long-term home parenteral nutrition adult patients, and patients with chronic kidney disease are particularly exposed and considered high-risk populations. Aluminum determination facilities are not usually available in most hospital scenarios; therefore, inadvertent high-aluminum concentrations might be provided. Efforts should be implemented to identify and subsequently reduce the amount of aluminum in parenteral solutions.

Background

As part of the quality standards in the care of patients hospitalized in neonatal, pediatric, and adult intensive care units (ICUs),[1] medical nutrition interventions have shown a positive of the metabolic, immune, and inflammatory responses that underlie the condition of critically ill patients.[2,3]

Despite a progressive decline in the prescriptions of parenteral nutrition (PN) admixtures in the past years, a significant

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percentage of patients still require administration of intravenous (IV) nutrients, which, even with the proven benefits, are not exempt from potential side effects and toxicity.[4-6]

One of the reported hazards of PN is the inadvertent and excessive provision of aluminum (Al), a condition especially described in low-birth-weight preterm infants (LBWPIs) and in patients with renal failure.[7]

Aluminum contamination is primarily derived from the glass containers of the components, required for the formulation of PN admixtures.[8,9] Commercial preparations of cysteine , calcium, and phosphate are reportedly the main sources of aluminum as a contaminant.[10-15]

Excessive intake of aluminum predisposes to osteomalacia, dementia, impaired neurocognitive development, encephalopathy, jaundice, and anemia.[9,10,15-19] The risk of aluminum toxicity depends on the dose, route of administration, and duration of exposure.[9] The greatest risk occurs when it is administered parenterally, in comparison with the enteral route, because in the former, intestinal regulatory mechanisms of absorption are bypassed.[10]

The Food and Drug Administration (FDA) has recommended limiting aluminum exposure from contamination of parenteral additives to <5 μg/kg/d.[20] However, in clinical practice, this amount is often exceeded.[8,10,16,21-25]

To our knowledge, in Mexico, no studies have addressed the amount of aluminum administered in PN admixtures, particularly in the neonatal population. The aim of this study was to determine the concentration of aluminum in theoretical formulated samples of PN admixtures, designed to be administered to LBWPIs, and to establish the potential toxicity risk of this mineral.

Methods

Commercial preparations of energy substrates, electrolytes, multivitamins, and trace elements usually employed for the formulation of PN admixtures as individual components were evaluated in this study. In addition, the theoretical aluminum content of 2 typical PN admixtures was estimated with regard to 2 hypothetical PN admixtures similar to the ones routinely prescribed in our neonatal unit.

Samples analyzed were randomly chosen from vials of sodium chloride, potassium phosphate, sodium acetate, sodium phosphate, magnesium sulfate, zinc sulfate, levocarnitine, multivitamin solution, selenium, cysteine hydrochloride, commercial trace element presentations, 10% crystalline amino acid solution, 20% lipid emulsion, and 50% dextrose.

In addition, from 2 formulations of PN admixtures (identical to the ones routinely prescribed for LBWPIs, with weights of 1800 g [admixture 1] and 1230 g [admixture 2]), patients' total daily intakes of aluminum were calculated from the sum of aluminum provided by each individual component and according to the volumes routinely prescribed to LBWPIs.

The total estimated aluminum amounts for each of the 2 admixtures were divided by the selected neonatal weights used for the formulations to obtain the theoretical clinical provision of aluminum expressed as μg/kg/min and to compare them with the safe thresholds established by the FDA.

In Mexico, phosphate is usually provided as potassium phosphate. To compare potential differences in aluminum content between potassium phosphate and sodium phosphate, we performed 2 different aluminum estimations, one using potassium phosphate as the main phosphate source and the other by substituting the former with sodium phosphate.

Aluminum determinations were performed at the Institute of Metallurgy from the University of San Luis Potosi, Mexico.

Aluminum Determination

The method used to measure levels of aluminum was derived from D'Haese et al.[26] Aluminum concentrations were determined by flame atomic absorption spectrometry (Model 3110; Perkin-Elmer, Waltham, MA) with a nitrous oxide–acetylene flame (temperature, 2600–2800°C). An aluminum hollow cathode lamp (Perkin Elmer) was used for the measurements at 309.3 nm, slit 0.7 nm. Aluminum concentrations in the samples were interpolated using a calibration curve (range, 2–20 ppm). Standard solutions were prepared from a commercial standard of aluminum (Perkin Elmer) (1000 mg/L^{-1} in HNO_3), using deionized water as dissolvent (Millipore, Billerica, MA). Detection limit was 1 mg/L^{-1}. Calibration method and instrumental conditions were optimized for this study. To avoid aluminum contamination, all laboratory materials were in plastic (polyethylene) and immersed in HNO_3 for 48 hours and washed with deionized water. Aliquots were taken directly from the original vials of each component analyzed.

All measurements were performed in triplicate from the same batch; sodium phosphate and levocarnitine were tested just in 1 sample due to institutional restrictions in availability. Reported results correspond to mean ± standard deviation.

Results

Calcium gluconate, potassium phosphate, trace elements, levocarnitine, and L-cysteine were positive for the presence of aluminum in the 3 processed commercial batches. The single sample of sodium phosphate analyzed was also positive for aluminum. Table 1 shows the individual components analyzed and their aluminum concentrations.

Table 2 shows the total aluminum content of the 2 typical PN admixtures, derived from the sum of the theoretical aluminum content of individual components administered according to the required volume.

According to the amount of aluminum measured in phosphate salts, individual aluminum provision from phosphate salts can be reduced by 52.7% by replacing potassium phosphate with sodium phosphate salts (Table 3).

Theoretically, replacing potassium phosphate with sodium phosphate in the 2 typical PN admixtures would reduce the

Table 1. Aluminum Concentration of Parenteral Nutrition Individual Components.

Components Evaluated: Generic (Trade Name, Manufacturer)	Lot of Commercial Product	Aluminum Concentration, Mean (SD), mg/L
20% Lipid emulsion MCT/LCT (SMOF lipids, Fresenius Kabi, Austria)	160K0090	ND
50% Dextrose (SOLUCION D-50, PISA Farmaceutica, Mexico)	A024551	ND
10% Crystalline amino acids (LEVAMIN PAD, PISA Farmaceutica)	J3L027	ND
Intravenous multivitamin solution (MVI-12 pediatric, Grossman, Mexico)	84152	ND
Sodium acetate (SOLUCION AC-S, PISA Farmaceutica)	C113125	ND
Intravenous trace elements[a] (TRACEFUSIN, PISA Farmaceutica)	C091852	2.3 (0.18)
Selenium (SELEFUSIN, PISA Farmaceutica)	C034246	ND
Zinc sulfate (ZN-FUSIN, PISA Farmaceutica)	C014202	ND
L-cysteine (FISCARNAT, PISA Farmaceutica)	C013601	2.56 (0.39)
Magnesium sulfate 20% (MAGNEFUSIN, PISA Farmaceutica)	B052773	ND
Sodium chloride 17.7% (SOLUCION CS-S 17.7%, PISA Farmaceutica)	B14A369	ND
Potassium phosphate (FP-20, PISA Farmaceutica)	B042654	3.78 (0.45)
Sodium phosphate (FOSFUSIN, PISA Farmaceutica)	C14Y347	1.78[b]
Calcium gluconate 10% (SOLUCION GC 10%, PISA Farmaceutica)	B013298	3.89 (0.37)
Potassium chloride (KELEFUSIN, PISA Farmaceutica)	B034325	ND
Levocarnitine (EFE-CARN, PISA Farmaceutica)	B014218	1.10[b]

LCT, long-chain triglyceride; ND, not detected; MCT, medium-chain triglyceride.
[a]Intravenous trace elements (TRACEFUSIN, PISA Farmaceutica): each 100 mL contains zinc chloride, 55 mg; copper sulfate, 16.90 mg; manganese sulfate, 38.10 mg; sodium iodide, 1.30 mg; sodium fluoride, 14.0 mg; and sodium chloride, 163.90 mg.
[b]Sodium phosphate and levocarnitine were tested just in 1 sample.

Table 2. Aluminum Daily Intake for 2 Hypothetical Neonates According to the Sum of the Amounts of Aluminum Detected in Individual Parenteral Nutrition Components, Underscoring, for Admixture 2, Aluminum Content That Surpassed the FDA Safe Maximal Aluminum Threshold.

Component	Volume, mL	Aluminum Content, µg	Aluminum Intake, µg/kg/d
Admixture 1 (hypothetical weight = 1800 g)			
50% Dextrose	37	—	—
10% Crystalline amino acids	21.4	—	—
Sodium chloride 17.7%	2.9	—	—
Potassium phosphate	0.7	3.01	2.82
Magnesium sulfate 20%	0.5	—	—
Calcium gluconate 10%	1.3	5.07	1.67
Selenium	0.1	—	—
Zinc sulfate	0.1	—	—
Multivitamins	0.3	—	—
Water	105	—	—
Total contribution		8.08	4.49
Admixture 2 (hypothetical weight = 1230 g)			
50% Dextrose	31.8	—	—
10% Crystalline amino acids	43	—	—
20% Lipid emulsion MCT/LCT	12.3	—	—
Sodium chloride 17.7%	1.2	—	—
Potassium phosphate	1.2	5.16	4.2
Magnesium sulfate 20%	0.3	—	—
Calcium gluconate 10%	2.4	9.36	7.61
Selenium	0.1	—	—
Zinc sulfate	0.2	—	—
Multivitamins	2.4	—	—
Water	89.1	—	—
Total contribution		14.52	11.8

FDA, Food and Drug Administration; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; —, not detected.

Table 3. Effect of Substitution of Potassium Phosphate (KPO_4) Salts With Sodium Phosphate ($NaPO_4$) Salts in Aluminum Parenteral Nutrition Admixture Contents.

Characteristic	mL	Aluminum per mL	Aluminum Content, µg	Total Aluminum Content, µg	Aluminum, µg/kg/d
Admixture for neonate 1, hypothetical weight 1800 g					
Original admixture with KPO_4					
KPO_4	3.78	0.7	2.64[a]		1.47
Calcium gluconate 10%	3.89	1.3	5.06[b]		2.81
				7.70[c]	4.27[d]
Substituting KPO_4 with $NaKPO_4$					
$NaPO_4$	1.78	0.7	1.25[a]		0.69
Calcium gluconate 10%	3.89	1.3	5.06[b]		2.81
				6.31[c]	3.50[d]
Admixture for neonate 2, hypothetical weight 1230 g					
Original admixture with KPO_4					
KPO_4	3.78	1.2	4.53[a]		3.68
Calcium gluconate 10%	3.89	2.4	9.34		7.6[e]
				13.87[f]	11.27[g]
Substituting KPO_4 with $NaKPO_4$					
$NaPO_4$	1.78	1.2	2.14[a]		1.74
Calcium gluconate 10%	3.89	2.4	9.34		7.6[e]
				11.48[f]	9.33[g]

[a]Percent reduction in aluminum content derived from phosphate salts, 52.7%.
[b]Percent reduction in total aluminum content, 18.1%.
[c]Calcium gluconate, main source of aluminum.
[d]Aluminum intake, below Food and Drug Administration (FDA) recommendations.
[e]Calcium gluconate, main source of aluminum.
[f]Percent reduction in total aluminum content, 17.2%.
[g]Aluminum intake, exceeding FDA recommendations.

final aluminum concentration by 18.1% and 17.2% for admixture 1 and admixture 2, respectively. Nevertheless, total content of aluminum was still found outside the safety margins recommended by the FDA in admixture 2, with calcium gluconate as the main source of aluminum contamination.

Discussion

Aluminum contamination in PN admixtures remains an unsolved problem.[11,27] Given its potential implications, in terms of morbidity and long-term side effects, physicians who care for patients with risk of aluminum toxicity must be aware of the potential sources of excessive amounts of this element.[28]

In the present analysis in Mexico and in accordance with previous international reports, calcium and phosphate salts, levocarnitine, cysteine, and trace elements are the main sources of contamination of aluminum,[12] so that neonatal PN routinely exceeds the upper safety limit established by the FDA of <5 µg/kg/d for aluminum provision.[20] Sodium phosphate salts also were positive for aluminum contamination but contained nearly 50% less compared with potassium phosphate.

The importance of preventing aluminum toxicity derives from the adverse effects that have been extensively described in patients receiving PN for prolonged periods, with particular emphasis on the neonatal or pediatric population, in whom renal excretion mechanisms are still immature[27]; hence, exposure to high concentrations of aluminum, usually inadvertently, can have toxic side effects.[11]

The association between exposure to aluminum and impaired neurodevelopment is well documented. Bishop et al[17] reported a cohort of preterm infants who received PN with concentrations up to 45 µg/kg/d; surviving infants were evaluated at age 18 months, and the authors noticed patients previously exposed to higher aluminum doses had lower neurodevelopment scores compared with infants receiving PN with concentrations of aluminum no greater than 5 µg/kg/d. Subsequently, the same authors documented the presence of high concentrations of aluminum in the central nervous system in an infant who previously received high aluminum concentrations in a PN solution.[29] This finding confirms the deleterious role of aluminum in neurocognitive development, particularly in susceptible populations such as LBWPIs.

Another potential and serious negative effect of aluminum toxicity is the role it exerts in bone metabolism. Metabolic bone disease (MBD), defined as the presence of patchy osteomalacia, bone pain, reduced bone turnover, and suppressed parathyroid hormone secretion,[10,30] represents a multifactorial entity[31] and is the result of several risk factors usually present in critically ill patients, including infants. These include vitamin D and vitamin

K deficiency, metabolic acidosis, immobility, lack of sun exposure, and inadequate intake of calcium and phosphate.[32]

Preventing aluminum toxicity might contribute to reducing the incidence of MBD in high-risk populations.[19] Excess of aluminum accumulates in bone mineralization fronts, affecting new bone formation and increasing osteoblast activity,[10,19,33-35] an aspect particularly relevant in pediatric and neonatal populations,[10] since preterm infants receiving PN longer than 3 weeks have 10 times higher bone aluminum concentrations compared with infants who receive enteral nutrition, predisposing them to develop osteomalacia.[35,36]

Current guidelines for bone metabolic disease prevention underscore the aluminum contamination from PN solutions as a preventable risk factor for osteomalacia, and the reduction of excessive aluminum intake should be pursued as a preventive measure.[37]

Aluminum toxicity has also been implicated as a risk factor for cholestasis in patients receiving PN regimens.[11] Alemmari et al[38] demonstrated the role of aluminum in the development of intestinal failure–PN-associated liver disease (IF-PNLAD), a clinical and biochemical entity highly prevalent in neonatal populations.[39]

The role of aluminum for the development of IF-PNLAD is related to mechanisms such as oxidative stress, lipid peroxidation, and DNA damage.[11] In experimental models, reducing the intake of aluminum and adding taurine have successfully prevented the presentation of liver complications associated with the use of PN.[40,41]

In clinical practice, several strategies to reduce aluminum intake from PN admixtures have been established. Diverse authors support the recommendation to substitute calcium salt presentations employed in the parenteral nutrition compounding, preferring the form of calcium chloride instead of calcium gluconate.[14,25,42]

Calcium chloride salts have lower contents of aluminum as a contaminant and could help to reduce final aluminum content by 34%.[42,43] Others authors have doubts about the utility of this intervention, under the rationale that excessive chloride may be a risk for the development of metabolic acidosis, an associated factor also involved in the development of MBD; in addition, calcium chloride also can affect calcium availability and the interaction with phosphate.[10,42]

In our study, we found that calcium gluconate is the main source of aluminum contamination. In Mexico, calcium salts are available only in the form of calcium gluconate, which show high aluminum content. From our findings, we postulate that the incorporation of chloride salts could be an attractive field of research to explore in our context as an additional way to reduce aluminum parenteral intake, particularly in LBWPIs.

Replacing potassium phosphate salts with sodium phosphate also represents a valuable measure to reduce the contribution of aluminum.[42] Sodium phosphate salts have a lower aluminum content compared with potassium phosphate, and their effectiveness has been widely documented.[11]

In our trial, we demonstrated that sodium phosphate salts can be considered a feasible substitute of potassium phosphate salts as a low-aluminum component in PN, leading to a reduction in aluminum content, derived from phosphate salts, by more than half.

In addition, aluminum contamination can be reduced by replacing glass burettes and syringes with plastic materials and by choosing commercial preparations of electrolytes and trace elements in plastic (polyethylene) vials instead of glass.[44] The rationale is supported by extensive evidence that shows glass contains more aluminum impurities in comparison with plastic.[27,45] We could not evaluate such an alternative, because all the PN components we tested were originally contained in glass vials. Electrolyte salts contained in plastic vials should be evaluated to confirm whether plastic containers provide lower amounts of aluminum.

Theoretical calculations of aluminum intake were performed according to 2 low-birth-weight preterm requirements. Although PN admixtures calculations were derived just from 2 hypothetical low-birth-weight infants, we confirmed that variations in body weight and in the requirements for calcium and phosphate were the main determinants related to exceeding the safety limit for daily intake of aluminum due to the volume of additives used.[46] The PN admixture, designed for very low-birth-weight preterm infants, represented the greatest risk for exceeding safe FDA aluminum intake thresholds.

Although only 2 sample PN admixtures as a finished product were evaluated and with a limited number of individual components, this study allows us an initial approach to establish the safety of the use of commercial products available in Mexico for the preparation of PN admixtures and to know their aluminum contents.

Limitations

We are aware that other medications also given to preterm infants, such as antibiotics, steroids, vasoactive amines, diluents, and loop diuretics, were not evaluated and might serve as unrecognized and potential sources of aluminum.[9,47]

The PN admixtures analyzed did not contain cysteine or trace elements, additives in which aluminum has been found as a contaminant. In diverse clinical scenarios, the addition of these products could potentially increase aluminum content and exceed the upper safe threshold proposed by the FDA (<5 μg/kg/d).[20]

No serum, tissue, or bone aluminum determinations were performed in infants receiving PN.[10,24,48,49] Preterm infants are not exempt from receiving aluminum from other sources and are exposed to the risk of developing aluminum-related long-term complications, even when PN admixtures are reduced in aluminum content. Aluminum determination facilities are not widely available in most hospital scenarios, so choosing products labeled as having a low aluminum content would help to reduce aluminum exposure.[28,50]

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