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CLINICAL INVESTIGATION

Aluminum in Pediatric Parenteral Nutrition Products: Measured Versus Labeled Content

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OBJECTIVE Aluminum is a contaminant in all parenteral nutrition solutions. Manufacturers currently label these products with the maximum aluminum content at the time of expiry, but there are no published data to establish the actual measured concentration of aluminum in parenteral nutrition solution products prior to being compounded in the clinical setting. This investigation assessed quantitative aluminum content of products commonly used in the formulation of parenteral nutrition solutions. The objective of this study is to determine the best products to be used when compounding parenteral nutrition solutions (i.e., those with the least amount of aluminum contamination).

METHODS All products available in the United States from all manufacturers used in the production of parenteral nutrition solutions were identified and collected. Three lots were collected for each identified product. Samples were quantitatively analyzed by Mayo Laboratories. These measured concentrations were then compared to the manufacturers' labeled concentration.

RESULTS Large lot-to-lot and manufacturer-to-manufacturer differences were noted for all products. Measured aluminum concentrations were less than manufacturer-labeled values for all products.

CONCLUSIONS The actual aluminum concentrations of all the parenteral nutrition solutions were significantly less than the aluminum content based on manufacturers' labels. These findings indicate that 1) the manufacturers should label their products with actual aluminum content at the time of product release rather than at the time of expiry, 2) that there are manufacturers whose products provide significantly less aluminum contamination than others, and 3) pharmacists can select products with the lowest amounts of aluminum contamination and reduce the aluminum exposure in their patients.

INDEX TERMS aluminum, parenteral nutrition, toxicity

ABBREVIATIONS FDA, Food and Drug Administration; PN, parenteral nutrition

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INTRODUCTION

Aluminum is the most abundant metallic element on earth and is naturally occurring in certain minerals, ores, oxides, and silicates. Humans are exposed to aluminum on a regular basis through drinking water, various foods, medications, dust, and deodorants. In an average, healthy individual, aluminum exposure causes little harm as a result of pharmacokinetic properties characterized by a poor oral bioavailability. The gastrointestinal tract allows less than 1% of ingested aluminum into the bloodstream. Renal excretion removes 99% of the aluminum that enters the bloodstream.[1] Despite these protective mechanisms, aluminum toxicity has been documented in the medical literature for over 30 years.[1–8] Recorded manifestations of aluminum toxicity include fracturing osteomalacia and reduced bone mineralization, neurological dysfunction and dialysis encephalopathy, microcytic hypochromic anemia, and cholestasis. Parenteral

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nutrition (PN) has long been implicated as a major source of aluminum exposure as a result of contamination of the component ingredients. These component products are contaminated with aluminum in raw materials as well as through byproducts from the manufacturing process, during which aluminum leaches from glass vials during autoclaving.[9–11] Patients at greatest risk for aluminum toxicity from PN include those with underlying renal dysfunction and prolonged courses of parenteral nutritional support. Premature infants are particularly at high risk of aluminum accumulation and toxicity as they often require days of PN support and have immature kidneys that are incapable of excreting aluminum efficiently. Calcium gluconate and phosphate salts are known to be especially high in aluminum content and are often administered to premature infants in substantial amounts to promote bone mineralization.[9,12]

In an attempt to limit the risk of aluminum toxicity, the U.S. Food and Drug Administration (FDA) modified its "Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parental Nutrition" with the January 2000 Final Rule, enacted in July 2004.[13,14] The Final Rule limits the aluminum concentration of large-volume parenteral products to 25 mcg/L. Small-volume parenteral products must state the maximum aluminum concentration at the time of product expiry on the product's label, but no maximum aluminum concentration is otherwise specified. Manufacturers of all PN products must also include a package insert with a standardized warning describing the presence of aluminum in the product; the risk of using the products in infants and patients with impaired kidney function; and a recommended maximum daily aluminum dose of 4 to 5 mcg/kg/day to prevent accumulation and toxicity.

The purpose of this study was to quantitatively determine the actual aluminum concentrations of all commercially available products used to prepare PN solutions from all available manufacturers and to determine the best (least contaminated with aluminum) products on the market.

METHODS

The Stanford University Medical Center Institutional Review Board approved this study. PN products available in the United States from all manufacturers were identified and collected for evaluation. Three separate lots from each manufacture of the following products were tested: sterile water for injection, dextrose 70%, amino acids, fat emulsion, calcium gluconate, sodium phosphate, potassium phosphate, potassium acetate, magnesium sulfate, sodium acetate, potassium chloride, sodium chloride, selenium, zinc chloride, zinc sulfate, pediatric multivitamins, and pediatric trace elements. The largest available product size was selected among products available in multiple sizes from the same manufacturer. Samples were prepared by drawing 2 mL of each solution into 3-mL Monoject syringes fitted with aluminum-free needles. Samples were transferred into metal-free transport tubes, each assigned with a code identifiable by investigators. Quantitative aluminum analysis was performed by the Mayo Clinic Laboratories (Rochester, MN) using inductively coupled plasma mass spectrometry conducted on a Perkin-Elmer Elan 6100 DRC II inductively coupled plasma mass spectrometer (PerkinElmer Life and Analytical Sciences Inc, Waltham, MA). Aluminum concentrations were reported to the investigators in "mcg/L" units. The Student's *t*-test was used to determine the statistical difference between the aluminum concentration on the manufacturer's labels and the mean measured aluminum concentration.

RESULTS

A total of 18 PN components consisting of 33 products from 6 available manufacturers in the States were sampled. The measured and labeled aluminum contents of the 33 products, along with days from expiry and p-values, are listed in Tables 1 through 3. Among all manufacturers, there was large lot-to-lot variability, but even more striking was the manufacturer-to-manufacturer difference between products.

The measured aluminum concentrations were significantly lower ($p<0.05$) than the labeled concentrations in all products except sodium chloride 2.5 mEq/L. All of the calcium gluconate and potassium phosphate products contained high amounts of aluminum in both the measured and labeled concentrations. Likewise, the labeled and measured concentrations of aluminum in the American Regent sodium phosphate product contained a high concentration of aluminum. Although these products contain the highest aluminum concentration, calcium gluconate, potassium phosphate, and sodium phosphate contained 20% to 30%, 8% to 16%, and 13% to 16% of the aluminum, respectively, compared to the labeled concentrations. Sterile water, amino acids, fat emulsion, potassium chloride, sodium chloride, 70% dextrose, sodium acetate, potassium acetate, magnesium sulfate, trace elements, multivitamin, zinc chloride, zinc sulfate, and selenium all had low aluminum concentrations.

Table 1. Aluminum Content of Various Products Used in Parenteral Nutrition Solutions

	Manufacturer (NDC)	Days From Expiry (Range)	Mean Aluminum Content (mcg/L)		p-Value
			Labeled	Measured (Range)	
Sterile water	American Regent (0517-3050-25)	1270 (1239-1299)	≤25	<5 (<5)	<0.0001
	American Pharmaceutical Partners (63323-185-50)	511 (356-666)	≤25	5 (<5)	<0.0001
	Hospira (0409-7990-09)	584 (507-635)	≤25	6.6 (<5-10)	0.0004
	B. Braun (0264-7850-00)	786 (702-844)	≤25	<5 (<5)	<0.0001
	Baxter (0338-0013-08)	241 (215-270)	25	<5 (<5)	<0.0001
Dextrose 70%	Hospira (0409-7120-07)	642 (625-661)	25	14 (11-16)	0.02
	B. Braun (0264-1290-50)	239 (50-427)	≤25	20 (19-21)	0.001
Amino acids, TrophAmine 10%	B. Braun (0264-9341-55)	579 (539-599)	≤25	7 (<5-11)	0.0008
Fat emulsion, intralipid 20%	Fresenius Kabi (0338-0519-03)	377 (209-507)	25	11 (<5-17)	0.05
Calcium gluconate, 100 mg/mL	American Pharmaceutical Partners (63323-311-61)	583 (570-599)	9400	2812 (1969-3495)	0.004
	American Regent (0517-3900-25)	416 (415-417)	12,500	2487 (1928-2887)	0.0008
Magnesium sulfate 50%	American Pharmaceutical Partners (63323-064-20)	234 (81-386)	300	109 (99-199)	0.03
	Hospira (00409-2168-03)	360 (296-417)	280	122 (103-134)	0.004
	American Regent (0517-2650-25)	552 (537-580)	12,500	165 (113-201)	<0.0001

NDC, National Drug Code

DISCUSSION

There have been numerous reports[1–8] of aluminum toxicity resulting from the contamination of PN solutions over the past 3 decades. A key study by Bishop et al.[5] that contributed to the FDA's decision to have PN solutions labeled with their aluminum content compared neurological development in premature infants who received a standard PN formula or an aluminum-depleted formula for a period of 5 to 16 days. The median aluminum content in the standard PN, 45 mcg/kg/day, was compared with that of an aluminum-depleted PN solution with an aluminum content of 4 to 5 mcg/kg/day. The authors estimated that for infants receiving the standard PN solution, the expected reduction in the Bayley Mental Development Index score would be 1 point per day of PN. A follow-up study of these former infants looked at their bone mineralization 15 years later.[6] Dual-energy radiograph absorptiometry showed that the now-adolescent patients who had received the aluminum-depleted PN solutions during prematurity had a higher bone mineral content and bone area than did those who received the standard PN solution. These findings indicate that total aluminum exposure from prolonged PN is a contributing factor in adverse neurologic and bone development among premature infants.

Since the FDA modified its regulations in 2000, several studies[15,16] have demonstrated that manufacturers are not able to meet these stricter

Table 2. Aluminum Content of Potassium and Sodium Products Used in Parenteral Nutrition Solutions

Product (Concentration)	Manufacturer (NDC)	Days from Expiry (Range)	Mean Aluminum Content (mcg/L)		p-Value
			Labeled	Measured (Range)	
Potassium phosphate (3 mmol/mL)	Hospira (0409-4201-01)	435 (387-482)	51,000	4040 (3647-4434)	0.005
	American Regent (0517-2350-25)	290 (203-327)	62,500	9972 (6512-16,818)	0.004
Potassium acetate (2 mEq/mL)	Hospira (0409-3294-06)	350 (296-417)	200	22 (11-42)	0.003
	American Regent (00517-2400-25)	495 (368-610)	25,000	744 (521-1120)	<0.0001
Potassium chloride (2 mEq/mL)	American Pharmaceutical Partners (63323-967-30)	282 (276-387)	100	6.5 (<5-8)	0.01
	Hospira (00409-1513-02)	116 (31-174)	100	5.3 (<5-6)	<0.0001
Sodium phosphate (3 mmol/mL)	Hospira (0409-7391-72)	479 (360-568)	180	29 (17-38)	0.001
	American Regent (00517-3450-25)	378 (296-451)	25,000	3242 (3177-3281)	<0.0001
Sodium acetate (2 mEq/mL)	Hospira (00409-1513-02)	400 (276-478)	360	73 (54-85)	0.0001
	American Regent (0517-2500-25)	525 (396-610)	25,000	103 (74-138)	<0.0001

NDC, National Drug Code

Table 3. Aluminum Content in Multivitamins and Trace Elements

	Manufacturer (NDC)	Days From Expiry (Range)	Mean Aluminum Content (mcg/L)		p-Value
			Labeled	Measured (Range)	
Zinc chloride (1 mg/mL)	Hospira (0409-4090-01)	411 (386-451)	150	11 (5-18)	0.0007
Zinc sulfate (1 mg/mL)	American Regent (0517-6110-25)	604 (568-635)	2500	249 (54-359)	0.002
Selenium (40 mcg/mL)	American Regent (0517-6510-25)	481 (386-549)	2500	285 (106-599)	0.005
Pediatric trace elements	American Regent Multitrace-4 (0517-9310-25)	518 (518)	2500	101 (101)*	NS
	American Regent Pediatric Trace Elements (0517-9203-25)	442 (386-518)	5000	574 (316-739)	0.0009
Pediatric multivitamin	Baxter (54643-5647-0)	261 (239-306)	30	28 (26-29)	0.1
	Hospira (61703-421-53)	99 (56-123)	42	18 (14-25)	0.02

NDC, National Drug Code; NS, not specified.
** Only 1 lot was sampled for this product.*

regulations. This is particularly true in premature infants because of their higher calcium and phosphate requirements compared to adults. A 2006 study by Poole et al.[15] calculated the expected daily aluminum exposure from pediatric PN solutions based on the manufacturer-stated aluminum concentration. Even when selecting products allegedly containing the lowest aluminum concentration, expected average aluminum exposure in infants was 59.9 mcg/kg/day, exceeding the FDA recommended limit by a 12-fold measure. The FDA's recommended limit of 5 mcg/kg/day was only feasible in patients weighing over 50 kg. In a 2010 follow-up study by Poole et al.,[16] the measured aluminum content of compounded PN solutions was found to be significantly less than the calculated content from the manufacturer's label. Despite this, aluminum assays of compounded neonatal PN solutions still exceeded the FDA limit of 5 mcg/kg/day by 3 to 5 times. As part of this study, 16 standard PN solution components were measured to determine each of the components' aluminum concentrations. The study reported that there were significant differences in the measured aluminum concentrations compared to the manufacturers' labeled concentrations. Our study validates these earlier findings that there is significantly less aluminum in PN solution components.

A study by Mouser et al.[17] found that 81% of aluminum contamination in neonatal PN was attributed to calcium gluconate. It is widely known that solutions such as calcium gluconate, sodium phosphate, and sodium acetate form complex ions with aluminum in the glass containers during the manufacturing process.[10,11] The findings in this study support previous reports that calcium and phosphate solutions contain high concentrations of aluminum compared to other solutions. Since calcium is the major contributor to aluminum contamination, methods of producing calcium gluconate in nonglass containers or the development of methods to combine calcium gluconate with calcium chloride or calcium acetate in the compounding process would likely decrease the level of aluminum contamination.[18,19] Our study was not powered or designed to serially monitor the aluminum concentration as the product remained in glass containers and neared its expiration date. This may be worth investigating in future studies to see if there is a significant change in aluminum concentration over the shelf life of the product.

The manufacturer-to-manufacturer variation in aluminum content of the PN solutions, as found in this study, indicates that the different processing methods of these solutions during manufacturing can considerably alter the degree of aluminum contamination of PN solutions. De Oliveira et al. recently demonstrated that aluminum contamination can occur throughout the formulation of aluminum-containing infusions, but that 56% of the aluminum content came from the commercial products prior to any manipulation in the hospital setting.[20] These studies again illustrate the need for changes in the manufacturing process for PN solution components. Manufacturers must find ways to more precisely label the aluminum content of PN products since the current labeling of concentrations that will not be exceeded at the product's expiry does not allow health professionals to properly assess the aluminum exposure in their patients. A more precise method may require manufacturers to label their products with the actual aluminum content at the time of product release rather than at the time of expiry.

Health professionals and manufacturers need to develop better methods for decreasing the risk of aluminum toxicity and eliminating potentially long-term adverse effects, especially to infants who receive PN.[21,22] Additional studies are needed to determine whether the FDA's recommendation of less than 5 mcg/kg/day is attainable when the least-contaminated products are used to make PN solutions. Data from this article need to be applied to actual PN patient orders to make this determination.

CONCLUSION

The actual aluminum concentrations of all of the PN solutions were significantly less than the aluminum contents based on the manufacturers' labels. These findings indicate that if manufacturers measure the actual aluminum content at the time of product release, this method may improve accuracy in labeling compared to an estimation at the time of expiry. These findings also show that there are manufacturers whose products result in less aluminum contamination than those of others. By identifying the least-contaminated products, pharmacists are able to choose products for their patients with the least amount of aluminum contamination and are thus able to reduce aluminum exposure and the potential for aluminum toxicity.

DISCLOSURE The authors have declared no potential conflicts or financial interest in any product or service mentioned in the manuscript.

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