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Aluminum Exposure From Pediatric Parenteral Nutrition: Meeting the New FDA Regulation

Robert L. Poole, PharmD[1]; Susan R. Hintz, MD[2]; Nicol I. Mackenzie, MD[3]; and John A. Kerner Jr, MD[2]

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Background: Aluminum toxicity can cause serious central nervous system and bone toxicities. Aluminum is a contaminant of parenteral nutrition (PN) solution components. Premature neonates requiring high doses of calcium and phosphate to mineralize their bones, children with impaired renal function, and children on PN therapy for prolonged duration are at the highest risk. Effective in July 2004, the U.S. Food and Drug Administration (FDA) mandated labeling requirements for aluminum content in all PN solution components. To assess the aluminum exposure in neonatal and pediatric populations, this study aims to determine patients' daily aluminum load (μg/kg/d) delivered from PN solutions. *Methods:* The study included all inpatients who received PN during calendar year 2006 (13,384 PN patient days). The calculated parameters of μg/kg/d and μg/L of parentally administered aluminum were stratified according to patient age and weight. Aluminum content by product and manufacturer were tabulated. *Results:* Forty-nine percent of the PN patient days were in patients weighing < 3 kg. These patients also received the largest amounts of aluminum (range, 30-60 μg/kg/d). Meeting the FDA regulation was possible only in patients weighing > 50 kg. *Conclusions:* Currently available parenteral products used to make PN solutions contain amounts of aluminum that make it impossible to meet the new FDA rule of < 5 μg/kg/d of aluminum exposure. Manufacturers must identify, develop, and adopt new methods to reduce the aluminum contamination in their products. Health care professionals should calculate aluminum loads in patients and make informed decisions when choosing PN products. (*JPEN J Parenter Enteral Nutr*. 2008;32:242-246)

Keywords: parenteral nutrition; pediatric; aluminum; toxicity; FDA regulation

Over the past 30 years, reports of aluminum toxicity have been cited in the medical literature discussing serious central nervous system, bone and liver damage, and anemia.[1-7] Specific findings of this toxicity include encephalopathy, dementia and impaired neurologic development, bone pain, osteopenia, osteomalacia, microcytic anemia, and cholestasis. Aluminum is the most abundant metal in our environment. Aluminum is found not only in raw materials but also is incorporated into products during the manufacturing process and from the leaching of aluminum from glass containers during autoclaving for sterilization.[8] It is introduced as a contaminant in products used to make parenteral nutrition (PN) solutions. Several defense mechanisms of the human body act to deter significant absorption of aluminum and effectively aid in its elimination. The GI tract, which typically allows < 1% of ingested aluminum into the bloodstream, is circumvented when PN is administered intravenously into the circulation. The elimination of aluminum occurs primarily via renal excretion. Accumulation and toxicity can be substantial in neonates who have immature kidneys and premature infants who have yet to mineralize their bones. Also at risk are children with renal failure on dialysis and infants and children who receive long-term PN therapy with high aluminum content.

In an effort to limit patients' exposure to aluminum and to prevent cases of aluminum toxicity, the U.S. Food and Drug Administration (FDA) amended its "Regulations on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition" with the January 2000 Final Rule. The implementation of the Final Rule was delayed several times to allow pharmaceutical

From [1]Lucile Packard Children's Hospital at Stanford, [2]Stanford University School of Medicine, Stanford, California, and [3]Monterey Medical Solutions, Inc, Salinas, California.

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Address correspondence to: Robert L. Poole, PharmD, Lucile Packard Children's Hospital at Stanford, Pharmacy Department, 725 Welch Road, Palo Alto, CA 94087; e-mail: rpoole@lpch.org.

manufacturers time to comply and was finally put into effect July 26, 2004.[9] The FDA now requires manufacturers of large- and small-volume parenterals, used in the preparation of parenteral nutrition solutions, to add certain information to their product's labels and package inserts.[10] Large-volume parenteral labeling must state that the product "contains no more than 25 mcg/liter" of aluminum. Although there is no specified limit for the aluminum content of small-volume parenterals or pharmacy bulk packages, the manufacturers are required to label their products with the maximum aluminum content at the product's expiry.

The FDA has also required that the following be included in the package insert for all products used in the preparation of PN solutions:

> **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 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Previous studies of aluminum exposure from PN solutions have reported aluminum intakes in the range of 10.8 - 60 μg/kg/d.[11-13] All of these studies exceeded the FDA's warning label amounts of 5 μg/kg/d. A key study by Bishop et al[4] that contributed to the FDA decision compared neurological development in 227 infants who were <34 weeks of gestational age, with a birth weight under 1850 g, who received a standard PN formula or an aluminum-depleted formula for a period of 5 - 16 days. The median aluminum content in the standard PN, 45 μg/kg/d, was compared to an aluminum-depleted PN solution with an aluminum content of 4 - 5 μg/kg/d. Bayley Mental Development Index (MDI) assessed neurologic development at a postterm age of 18 months. For the group of infants receiving the standard PN for >10 days, the MDI score was 10 points less than for those patients receiving the aluminum-depleted PN ($P = .02$).[4] The authors estimated that for infants receiving the standard PN solution, the expected reduction in the Bayley MDI score would be 1 point per day of intravenous feeding.

The purpose of our study was to calculate the daily amounts of aluminum that neonatal and pediatric patients at our institution would receive from parenteral nutrition solutions if they were made from currently available products labeled with the least aluminum content. Using those products would in theory minimize the patient's aluminum exposure. We also tested the feasibility of meeting the FDA's recommendation of limiting aluminum exposure to < 5 μg/kg/d. We did not measure serum aluminum concentrations or report any toxicities that may have occurred from aluminum loading in patients.

Methods

All pediatric inpatients who received PN at our institution during the calendar year of 2006 were identified through the pharmacy PN database and included in the study. The study patient population ranged in age from premature infants up to 18 years, regardless of patient weight. Patient data were stratified by weight, number of PN orders, and number of PN days per patient. To estimate the total aluminum exposure from PN, we collected the aluminum content of 114 marketed products used to prepare PN solutions. We then used the products with the lowest labeled aluminum content for our study. To estimate the minimum possible aluminum exposure per patient resulting from PN, the aluminum contents of these products were entered into the calculation files of our PN software. The PN software[14] used at our institution calculates the aluminum content of each patient's solution using the manufacturer's labeled concentrations and includes that data in the PN database. The database created by the software captures all aspects of each patient's daily PN therapy and provides a historical record for future studies. All aluminum calculations were based on the exact volume of PN ordered for each patient in mL/kg/d. The calculated daily aluminum load in μg/kg/d and μg/L was determined and stratified by the patients' weights.

Results

The study included 13,384 PN patient days in 1003 patients. Patient demographics are displayed in Table 1. We found that 49% of the PN days were among patients weighing <3 kg, the highest risk patient category.

The calculated aluminum exposure is listed in Table 2 by patient weight and includes the average aluminum exposure in μg/kg/d and the average amount of aluminum in μg/L. The most vulnerable patients, those weighing <3 kg, received the largest total daily dose of aluminum (range, 30.3-59.9 μg/kg/d). The calculated aluminum exposure in these infants was approximately 6-12 times the recommended safe amount.

Data from our institution from calendar year 2004 are presented in Tables 3 and 4 for comparison to the current 2006 study data (Tables 1 and 2). In 2004, there were 8334 patient days in 737 patients. Similarly, 41% of the PN days were in patients weighing <3 kg, and their calculated aluminum exposure ranged from 29.4 to 50.7 μg/kg/d (6-10 times the recommended safe amount).

Table 1. Patient Demographics, 2006 (n = 1003)

Weight, kg	No. of Patients	No. of Patient Days	Average Parenteral Nutrition Days/Patient	Range of Parenteral Nutrition Days/Patient
0-<1	34	1230	36.2	1-46
1-<2	237	3370	14.2	1-74
2-<3	192	1946	10.1	1-84
3-<4	187	1735	9.3	1-138
4-<5	46	435	9.5	1-97
5-<10	54	1048	19.4	1-177
10-<20	124	1555	12.5	1-93
20-<35	49	585	11.9	1-102
35-<50	31	506	16.3	1-91
50-<100	49	974	19.9	1-116

Table 2. Calculated Aluminum Exposure, 2006

Patient Weight, kg	Expected Average Aluminum Exposure, µg/kg/d	Parenteral Nutrition Average Solution Aluminum Concentration, µg/L
0-<1	59.9	248.0
1-<2	40.1	230.6
2-<3	30.3	226.2
3-<4	27.2	234.9
4-<5	22.8	218.4
5-<10	16.3	173.8
10-<20	12.3	178.6
20-<35	8.4	143.3
35-<50	8.1	190.8
50-<100	6.0	165.2

Table 3. Patient Demographics, 2004 (n = 737)

Weight, kg	No. of Patients	No. of Patient Days	Average Parenteral Nutrition Days/Patient	Range of Parenteral Nutrition Days/Patient
0-<1	23	577	25.1	1-27
1-<2	149	1594	10.7	1-67
2-<3	134	1205	9.0	1-64
3-<4	138	1486	10.8	1-80
4-<5	54	582	10.8	1-81
5-<10	74	866	11.7	1-78
10-<20	91	1143	12.6	1-76
20-<35	26	320	12.3	1-86
35-<50	21	279	13.3	1-36
50-<100	27	282	10.4	1-61

Table 4. Calculated Aluminum Exposure, 2004

Patient Weight, kg	Expected Average Aluminum Exposure, µg/kg/d	Parenteral Nutrition Average Solution Aluminum Concentration, µg/L
0-<1	50.7	245.8
1-<2	34.8	233.6
2-<3	29.4	239.3
3-<4	26.6	255.7
4-<5	23.8	230.8
5-<10	18.7	207.8
10-<20	13.5	182.0
20-<35	9.3	182.6
35-<50	7.5	185.5
50-<100	5.1	189.5

Table 5 shows the 23 products with the lowest labeled amounts of aluminum available on the market; these are the products used in this study. The results of our study showed that it was not possible to meet the FDA mandate when using currently available PN products with the lowest labeled aluminum content. Parenteral aluminum exposure from PN in amounts <5 µg/kg/d was possible only in patients weighing >50 kg. Premature infants, neonates, and children actively making bone have calcium and phosphate requirements that can lead to aluminum toxicity if they are receiving all of their nutrition parenterally.

Discussion

There have been numerous reports of aluminum toxicity from the contamination of PN solutions over the past 3 decades.[1-7] This led the FDA to require products used to prepare PN solutions be labeled with their aluminum content.

The results of our study showed that by using the products with the least amount of labeled aluminum content to prepare PN solutions, the FDA-recommended safe amount of 5 µg/kg/d could not be met. The patients at highest risk for aluminum toxicity are premature neonates who may have compromised renal function and also receive prolonged courses of PN therapy. The calculated aluminum exposure in the 6546 neonatal PN solutions (patient weights <3.0 kg) in our study exceeded the FDA limit by factors of 6-12 times (30 - 60 µg/kg/d). Smith et al[15] recently reported similar numbers (13 - 56 µg/kg/d) in their study of 8 neonatal PN solutions (patient weights <3.0 kg) in which the aluminum content was minimized in the same method as in our study.

There are still a number of concerns and considerations that must be addressed: (1) Patients are exposed to other therapies that also contain significant amounts of aluminum (eg, albumin, blood products, L-cysteine, and heparin),[16] and (2) there is also huge variability in the aluminum contamination of generic products from different manufacturers. Manufacturers must identify, develop,

Table 5. Aluminum Content of Parenteral Nutrition Component Solutions

Product	Container Size	Manufacturer[a]	Expected Aluminum Content at Expiry, µg/L
Amino acids			
TrophAmine 10%	500-mL bottle	B. Braun	<25
Aminosyn 10%	1000-mL bag	Hospira	<25
Aminosyn RF 5.2%	500-mL bag	Hospira	<25
Dextrose 70%	2000-mL bag	Hospira	<25
Fat emulsion 20%	100-mL bag	Fresenius Kabi	<25
Sterile water injection	3000-mL bag	Baxter	<25
Sodium acetate 2 mEq/mL	100-mL bulk	APP	100
Sodium chloride 2.5 mEq/mL	200-mL bulk	APP	<25
Sodium phosphate 3 mM/mL	50-mL SDV	APP	7050
Potassium acetate 2 mEq/mL	100-mL bulk	APP	50
Potassium chloride	250-mL bulk	Baxter	<25
Potassium phosphate 3 mM/mL	50-mL SDV	APP	21,000
Magnesium sulfate 50%	50-mL SDV	APP	105
Calcium gluconate 100 mg/mL	200-mL bulk	APP	4000
Multi Trace-4 pediatric	3-mL SDV	American Regent	5000
MVI pediatric	5-mL SDV	aaiPharma	42
MVI adult	10-mL SDV	Mayne	78
Vitamin K 1 mg/0.5 mL	0.5-mL amp	Hospira	100
Trace elements	50-mL bulk	Hospira	570
Zinc chloride 1 mg/mL	10-mL vial	Hospira	150
Selenium 40 µg/mL	10-mL SDV	APP	708
Copper chloride 0.4 mg/mL	10-mL vial	Hospira	3400
L-cysteine 50 mg/mL	50-mL vial	American Regent	5000

SDV, single-dose vial.
[a]aaiPharma, Lake Forest, Illinois; American Regent, Shirley, New York; APP, Schaumburg, Illinois; Baxter, Deerfield, Illinois; B. Braun, Bethlehem, Pennsylvania; Fresenius Kabi, Uppsala, Sweden; Hospira, Lake Forest, Illinois; Mayne, Lake Forest, Illinois.

and adopt new methods to reduce the aluminum contamination in their products. (3) The FDA ruling set no limits for the maximum amount of aluminum content in small-volume parenterals, yet they are the largest contributors to the problem. The FDA should reassess this issue. (4) Cost: are products with greater aluminum contamination cheaper? If so, they may also become the contracted bid item in use at your institution. Health care professionals must carefully evaluate the aluminum content of parenteral products to assess the potential for toxicity. (5) Are we overestimating the aluminum content in large-volume parenterals? By allowing manufacturers to label their products as "contains no more than 25 mcg/liter," calculated aluminum content may be greater than the actual content amount. Labeled amounts of aluminum are based on the highest aluminum concentration of the first 5 batches of product produced after the effective date of the rule.[9] Future studies must document actual measured amounts of aluminum and not calculated amounts, as the actual amounts vary from lot to lot based on raw materials and manufacturing processes. A preliminary study from the Cleveland Clinic[17] demonstrated that the actual aluminum exposure from PN solutions is significantly less than the estimated amount from calculations based on manufacturers' labels. Nineteen of their 20 patients had calculated aluminum exposures >5 µg/kg/d. In contrast, only 6 of their 20 patients (4 infants and 2 adults) had measured levels of aluminum in their PN solutions >5 µg/kg/d. More studies measuring actual aluminum content of PN solutions and manufacturers' products are needed.

Conclusions

Currently available parenteral products, used to make PN solutions for pediatric and neonatal patients, contain amounts of aluminum that make it impossible to meet the July 2004 FDA rule of <5 µg/kg/d of aluminum exposure. Manufacturers must identify, develop, and adopt new methods to reduce the aluminum contamination in their products. The FDA mandate allows clinicians to calculate the approximate aluminum exposure that patients may be receiving. However, we may be overestimating the

aluminum content in large-volume parenterals as manufacturers are allowed to label their products "contains no more than 25 mcg/liter" (of aluminum). The FDA did not set a maximum for the amount of aluminum allowable in small-volume parenterals, where the content may be very high (eg, calcium gluconate, potassium and sodium phosphates, potassium and sodium acetates). Manufacturers should be required to label their products with the actual aluminum content at product release and not with an estimate of what the concentration will be at the product's expiration date. The current labeling requirement places responsibility on health care professionals to calculate (or automate the calculations of) aluminum loads in patients, and to make informed decisions when choosing PN products.[16] Future studies should focus on determining the actual aluminum content of PN solutions compared with the calculated amounts based on PN product labels at expiry. Pharmacists should evaluate their PN process and select products with the lowest aluminum content to help prevent future cases of aluminum loading and toxicity in infants and children.

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