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Aluminum in Parenteral Nutrition Solution—Sources and Possible Alternatives*

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ABSTRACT. The extent of aluminum (Al) contamination in parenteral nutrition (PN) solutions for infants is not known. Aluminum was measured in 136 samples from various commercially available components that are used with PN. Results showed Al content varied widely among different components. The same chemical may have a different Al content depending on the manufacturer. However, Al contents were similar among lots from the same manufacturer for the same chemical. Aluminum contamination was arbitrarily classified as high (> 500 μg Al/liter), intermediate (51-500 μg Al/liter) or low (≤ 50 μg Al/liter). The high group included most calcium and phosphorus containing salts, 1 multivitamin preparation, folic acid, ascorbic acid and concentrated (25%) albumin. The intermediate group included sodium lactate, potassium phosphates, zinc and chromium chloride, multitrace metal preparation, and 5% plasma protein. The low group included amino acids, sterile water and dextrose water, chloride salts of sodium, potassium, calcium, copper and chromium, sodium phosphates, magnesium sulphate, zinc sulphate, vitamin B_{12}, vitamin K_1, 1 multivitamin preparation, soybean oil emulsion and heparinized (2 U/ml) saline. PN solutions made from high Al components may contain up to 300 μg Al/liter. Calcium gluconate contributed > 80% of the total Al load from PN. Lowering of Al content in calcium gluconate in addition to use of specific low Al components offers the opportunity to significantly lower the Al concentration of the final PN solution and theoretically may achieve an Al content as low as 12 μg/l. We speculate that Al contamination may occur because Al is present naturally in the chemical substance or added during the manufacturing process. (*Journal of Parenteral and Enteral Nutrition* **10:** 591–595, 1986)

Aluminum toxicity, particularly with respect to impaired bone mineralization, is well documented.[1–6] In humans, there are two major groups of patients at risk for aluminum toxicity, namely, renal failure patients on chronic dialysis,[1–3] and, patients receiving long-term parenteral nutrition.[4]

Although it is known that certain components of parenteral nutrition solution such as calcium and phosphate may be contaminated with aluminum,[7] there are no systematic data to document the extent of aluminum contamination from various components of parenteral nutrition solution and whether 'low' aluminum containing alternatives are available. This study therefore aimed to determine the extent of aluminum contamination of frequently used components of parenteral nutrition solutions used for infants; and, for components with high aluminum content, to explore whether there are alternatives with low aluminum content.

METHODS

Aluminum (Al) concentrations were determined from individual components of parenteral nutrition (PN) solution used for infants (Table 1). Each component was obtained from commercial sources. Certain components such as preservative-free heparinized saline not directly used for PN purposes but which may be used during the period of PN for catheter "flushing" were were also measured for Al concentration. In addition, needles with an Al hub were also tested for their potential to introduce Al contamination of the PN solution. This was tested by flushing 25 to 100 ml of Al-free water or dextrose water through the needle and measuring aliquots of the flushed solutions for Al.

Aluminum was measured by electrothermal (flameless) atomic absorption spectrophotometry.[8–10] The aluminum content was measured by the method of standard addition.[10] Both internal (Ortho Diagnostic Systems Inc, Raritan, NJ) and external (Robens Institute, University of Surrey, Guilford, UK) quality control samples were used to monitor this method. The intra- and inter-run coefficients of variation for the aluminum measurement are both 13%. Minimum detection limit of our assay is <5 μg aluminum/liter.

Data storage and calculation for mean and range of aluminum concentrations were performed with the CLINFO program of the National Institutes of Health, General Clinical Research Center, University of Cincinnati.

RESULTS

Aluminum (Al) concentration was measured in 123 samples from 16 different components (Table 1) that are used in parenteral nutrition (PN). In addition, aluminum

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TABLE I
Sources of aluminum contamination in parenteral nutrition solution

Products	Number tested sample/lot	Company	Aluminum (Al) μg/liter mean (range)		
			High >500 μg Al/liter	Intermediate 1–500 μg Al/liter	Low ≤50 μg Al/liter
A. Frequently used components					
Sterile water	3/3	Abbott			<5
Sterile water	2/2	McGaw			<5
Sterile water	2/2	Travenol			<5
Dextrose water (10, 20, 50%)	5/5	Abbott			<5
Dextrose water (10, 50%)	4/4	McGaw			<5
Dextrose water (5, 10, 50%)	4/4	Travenol			<5
Crystalline amino acids					
Aminosyn (5, 7, 10%)	6/6	Abbott			17 (<5–47)
Freamine (8.5%)	3/3	McGaw			12 (5–24)
Travasol (10%)	2/2	Travenol			7 (6, 8)
TrophAmine (6%)	2/2	McGaw			<5
Aminosyn PF (7%)	2/2	Abbott			10 (9, 11)
HepatAmine (8%)	1/1	McGaw			22
NephrAmine (5.4%)	1/1	McGaw			<5
Sodium salts					
Sodium chloride	3/3	Abbott			3 (<5–5)
Sodium acetate	1/1	Lyphomed			<5
Sodium phosphate	4/3	Abbott			6 (<5–16)
Sodium phosphate	3/2	Invenex	2236 (2026–2370)		
Sodium lactate	2/2	Abbott		184 (136,231)	
Potassium salts					
Potassium chloride	3/3	Abbott			4 (<5–11)
	1/1	IMS			17
	1/1	Elkins Sinn			<5
	2/2	Invenex			3 (<5, 5)
	2/2	Lyphomed			<5
Potassium acetate	2/1	Abbott			<5
Potassium phosphate	3/3	Abbott	2189 (2069–2301)		
	1/1	Invenex		92	
Calcium salts					
Calcium gluconate	3/3	Lyphomed	2245 (2000–2586)		
	2/2	Invenex	2601 (2592, 2610)		
	4/4	Elkins Sinn	3973 (1095–5565)		
	1/1	IMS	3299		
	1/1	American Quinine	2286		
Calcium gluceptate	2/1	Eli Lilly	3640 (3439, 3842)		
Calcium chloride	3/2	Elkins Sinn			15 (12–19)
	1/1	Lymphomed			5
	1/1	Abbott			5
Magnesium salts					
Magnesium sulphate	1/1	Abbott			5
	2/2	Invenex			3 (<5, 5)
	2/2	American Quinine			<5
Soybean oil emulsion					
Intralipid (10%)	2/2	KabiVitrum			<5
Intralipid (20%)	2/2				<5
Trace metals					
Zinc chloride	3/3	Abbott		99 (81–123)	
	1/1	Invenex			16
	1/1	Lyphomed			35
Zinc sulphate	1/1	Lyphomed			35
	1/1	Invenex			21
Copper chloride	3/3	Abbott			24 (5–37)
Chromium chloride	3/3	Abbott			21 (20–23)
	1/1	Lyphomed		78	
Zinc, copper, magnesese, chromium	1/1	Lyphomed		136	
Vitamins					
MVC 9+3	3/3	Lyphomed	897 (741–1018)		
MVI 12	3/3	Armour			17 (12–20)
Aquamephyton	3/3	Merck			8 (<5–25)
Folic acid	2/2	Lederle	1534 (1491, 1577)		
Vitamin B_{12}	2/2	Squibb			<5
Ascorbic acid	1/1	Invenex	1962		
	1/1	Skokie	1450		
	1/1	Roche	1168		

TABLE I—*Continued.*

Products	Number tested sample/lot	Company	Aluminum (Al) μg/liter mean (range)		
			High >500 μg Al/liter	Intermediate 1–500 μg Al liter	Low ≤50 μg Al liter
B. Infrequently used components or used intravenously alone					
Albumin (25%)	4/3	Armour	2364 (1116–5840)		
	1/1	Cryosan	914		
Plasma-Plex	2/2	Armour		53 (44, 62)	
Plasmanate	2/2	Cutter		137 (123, 150)	
Heparinized Saline (2 u/ml)	4/4	*			<5
C. 16-Gauge needle with aluminum hub	2/2	Monoject			+

* Prepared under sterile conditions in pharmacy using normal saline (Abbott Labs) and heparin (1000 U/ml, O'Neal, Jones and Feldman Company or 100 U/ml, Elkin Sinn Company).

† Did not alter aluminum concentration of flush solution (aluminum "free" water, 50% dextrose water).

was also measured in nine samples of protein containing colloid solution and in four samples of diluted heparinized (2 U/ml) saline which may be used in conjunction with PN. The degree of aluminum contamination was arbitrarily classified into high (> 500 μg Al/liter), intermediate (51–500 μg Al/liter) and low (≤ 50 μg Al/liter) ranges (Table I). The extent of aluminum contamination varied widely among different chemicals. Thus Al content varied from <5 μg/liter in sterile dextrose water to >5000 μg/liter in calcium gluconate. Al content also varied among different salts of the same chemical. Thus the Al content of calcium salts may range from <20 μg/liter in calcium chloride to >5000 μg/liter in calcium gluconate. Even the same product may have different degrees of aluminum contamination among different manufacturers, eg, 5-, 23-, and 373-fold differences from the lowest to the highest mean Al content for zinc chloride, potassium phosphates, and sodium phosphates, respectively. However, the Al concentrations for the same product were similar among lots from the same manufacturer.

The contribution from the various sources of aluminum in a high calcium and phosphorus PN solution tested for use in infants[11] is shown in Table II. The calculated Al content of this solution when prepared with high Al components may reach almost 300 μg/liter. Calcium gluconate contributed up to 88% of potential aluminum load in the PN solution. It is theoretically possible, that, by using available low Al components and calcium chloride as the source of calcium, a similar PN solution would have an estimated Al content as low as 12 μg/liter (Table II).

The aluminum needle hub did not increase the Al content of water or dextrose water flushed through these large bore needles (Table I).

DISCUSSION

Aluminum is the third most abundant naturally occurring element, and the most common metallic element, comprising approximately 8.8% of the earth's crust.[12] It is therefore not surprising that aluminum contamination is widespread. However it is apparent from this study that the extent of aluminum contamination of nutrient products varied widely. Certain products such as calcium gluconate are heavily contaminated with aluminum whereas other products, such as sterile water and dextrose water, are essentially aluminum free.

Since some products eg, calcium gluconate, from a number of manufacturers have similar degrees of aluminum contamination, the source of contamination may be from the aluminum present naturally in the chemicals. Variability in the aluminum concentration of other products such as sodium phosphates from different manufacturers would be consistent with either a variation in aluminum contamination of different sources or variation related to the manufacturing process. The consistent range of aluminum concentrations of the same product among different lots from the same manufacturer is consistent again with uniform contamination at the source or in the manufacturing processes. In the preparations of albumin solution for intravenous use, it has been reported that aluminum contamination originated from the extraction of filters and filter aids used to separate and clarify fractions obtained by the Cohn fractionation process. Alteration in the fractionation protocol was able to lower the aluminum contamination.[13] Thus at least in some instances, manufacturing process is a likely reason for aluminum contamination.

There is no known physiologic role for aluminum in animals and humans. In contrast, aluminum toxicity in human is well documented.[1-4,6] Markedly elevated aluminum accumulation in bone may occur after as short as 3 weeks of parenteral nutrition in infants,[7] supporting the thesis that infants receiving PN are at risk of aluminum toxicity. From our data, it would appear that even elimination of aluminum contamination from a few products, such as calcium and phosphorus containing salts, could have major impact in markedly lowering the aluminum content of the final PN solution, thus diminishing the potential toxic effects of aluminum.

All calcium gluconate and calcium gluceptate solutions tested had very high aluminum content. Calcium chloride is much less heavily contaminated with aluminum and theoretically could be used to replace calcium gluconate as a source of calcium. The major potential disadvantage with use of calcium chloride instead of calcium gluconate is the high chloride content (60 meq/liter) of the final PN solution. The resultant chloride intake would be at or above the maximum recommended daily allowance of 5.8 meq/kg for an infant ingesting 200 ml of milk/kg/day.[14] The theoretical risk of hyperchloremic acidosis

TABLE II
Distribution of aluminum (Al) in a "high calcium and phosphorus" parenteral nutrition solution

Infusate		High Al components	Parenteral nutrition solution			Low Al components	Parenteral nutrition solution		
Constituent	Content liter	μg Al/liter	Component (ml) added	Al (μg) added	% Al	μg Al/liter	Component (ml) added	Al (μg) added	% Al
Amino acid	25 g	15	500	7.50	2.60	15	500	7.50	68.74
Glucose ($D_{50}W$)	200 g	0	400	0.00	0.00	0	400	0.00	0.00
Water	to 1 liter	0	0	0.00	0.00	0	36	0.00	0.00
Sodium (Na)	25 meq	3 (as NaCl)	10	0.03	0.01	6 (as Na phosphates)	5	0.03	0.27
Potassium (K)	25 meq	2189 (as K phosphates)	5	10.95	3.80	4 (as KCl)	12.5	0.05	0.46
Calcium (Ca)	600 mg	3973 (as Ca gluconate)	64	254.27	88.26	15 (as $CaCl_2$)	22	0.33	3.02
Magnesium (Mg)	72 mg	5 (as Mg sulphate)	1.5	0.01	0.00	5 (as Mg sulphate)	1.5	0.01	0.09
Phosphorus (P)	465 mg								
Chloride (Cl)	31–60 meq†	4 (as KCl)	1.5	0.01	0.00	3 (as NaCl)	5	0.02	0.18
Zinc (Zn)	2 mg	99 (as $ZnCl_2$)	2	0.2	0.07	16 (as $ZnCl_2$)	2	0.07	0.64
Copper (Cu)	0.2 mg	24 (as $CuCl_2$)	0.5	0.01	0.00	24 (as $CuCl_2$)	0.5	0.01	0.09
Chromium (Cr)	2 μg	78 (as $CrCl_3$)	0.5	0.04	0.01	21 (as $CrCl_3$)	0.5	0.01	0.09
Multivitamin	‡	897	12.5	11.21	3.89	17	12.5	0.21	1.92
Phytomenadione	2 mg	8	0.2	0.00	0.00	8	0.2	0.00	0.00
Folate	3 mg	1534	0.6	0.92	0.32	1534	0.6	0.92	8.43
Vitamin B_{12}	50 μg	0	0.5	0.00	0.00	0	0.5	0.00	0.00
Ascorbic acid	0.5 g	1962	1.5	2.94	1.02	1168	1.5	1.75	16.04
Total			1000	288.09	100		1000	10.91	100

Maximum dextrose content = 12.5 g/dl for peripheral vein infusion, 20 to 25 g/dl for central vein infusion.

* Estimated from Table I. For those components in which the aluminum concentration was below the detection limit, their contribution to the aluminum contamination of the final solution were arbitrarily assigned as zero.

† High chloride content with use of calcium chloride.

‡ Multivitamins used: MVC 9 + 3 as high aluminum component and MVI 12 as low aluminum component.

may be unacceptable. It is possible to lower aluminum contamination and lower chloride load with the use of equal mixtures of calcium gluconate and calcium chloride; or the use of nonchloride salts of other cations eg, sodium or potassium acetate. Whether these changes in the composition could affect the solubility of calcium and phosphorus in the nutrient infusate and/or the acid-base status of the patients remains to be tested.

Heparin solutions have been reported to be quite heavily contaminated with aluminum.[7] However when prepared in concentrations suitable for use in infant, the actual aluminum load appears minimal. Our data on the extent and variability of aluminum contamination of other products eg, protein containing colloid solutions, not generally used as parenteral nutrition, but nevertheless used frequently in infants particularly for resuscitation purposes, supports the findings of other published data.[15]

The presence of aluminum in the hub of large bore needles used in the preparation of PN solution does not appear to contaminate the final solution, presumably because of the small surface area of contact and the short period of contact during which various components (amino acids, sterile water, and dextrose water) are transferred into the final bottle.

We conclude that aluminum contamination of nutrient products is widespread. This might occur as result of natural contamination or during the manufacturing process. The presence of low aluminum contaminated products are freely available with the exception of a suitable intravenous calcium preparation. Thus, if a low aluminum containing calcium source is available, it is possible to markedly lower the aluminum content of PN solution, thus minimizing the potential risk of aluminum toxicity in infants requiring parenteral nutrition.

ADDENDUM

The aluminum content of MVI Pediatrics (Armour Company) is 8 (6–9) μg/liter, *M* (range) of four samples from two lots.

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