Calculating aluminum content in total parenteral nutrition admixtures

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The Food and Drug Administration (FDA) rule for limiting aluminum content in total parenteral nutrition (TPN) preparations continues to cause concerns among health care professionals, especially pharmacists.[1] The federal regulation applies to drug manufacturers and not pharmacy practitioners and has three main objectives: (1) that the labels of all large- and small-volume parenterals used to prepare TPN formulations state the maximum aluminum concentration (in micrograms per liter) at expiration, (2) that the data submitted to FDA supporting the label claim must include information that describes a validated assay method for aluminum determination, and (3) that objectives 1 and 2 allow, but not mandate, health care professionals to calculate a patient's exposure to aluminum when receiving TPN and take actions that limit intake in patients susceptible to aluminum toxicity. The statement on clinical limits for aluminum levels required by FDA for inclusion in the package insert contains this warning: "Levels of aluminum at greater than 4 to 5 μg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity."[2] Although the FDA rule does not require pharmacists to intervene whenever a TPN formulation contains more aluminum than a daily dosage of 5 μg/kg, we believe that practicing pharmacists have a professional responsibility to calculate the daily aluminum load of compounded TPN preparations and that this information should be reported on the label of each admixture dispensed. Such calculations can be performed manually, but ideally the total aluminum content in a TPN preparation should be included in the software programs used for automated compounding devices.

Since Abbott Laboratories is already in compliance with FDA's mandate,[1] we calculated the theoretical aluminum exposure associated with its products (except for multivitamin injections) in clinically relevant nutrition support scenarios for infants and adults.[3,4] Table 1 lists the products used in these calculations; the volumes selected were based on components that would typically be used with automated compounding devices wherever possible. Data on the aluminum concentrations of

Table 1.
Aluminum Concentration in Parenteral Nutrition Additives

Additive	Volume (mL)	List No.	Maximum Aluminum Concentration (μg/L)
Aminosyn II 10%[a]	2,000	7121-07	25
Aminosyn PF 10%[a]	1,000	1617-05	25
Dextrose 70%[a]	2,000	7918-15	25
Liposyn III 20%[a]	500	9791-03	25
Sterile Water for Injection, USP[a]	2,000	7118-07	25
Sodium Chloride 23.4%, USP[a]	250	1130-02	100
Sodium Phosphates, USP[a]	50	3295-51	28,000
Sodium Acetate 16.4%, USP[a]	100	3299-06	360
Potassium Chloride Concentrate, USP[a]	250	1513-02	100
Potassium Acetate 19.6%, USP[a]	100	3294-06	200
Calcium Gluconate 10%, USP[a]	10	1184-01	12,000
Magnesium Sulfate 50%, USP[a]	50	2168-03	280
Trace Elements 4, USP[a]	50	4592-50	570
Cysteine Hydrochloride, USP[a]	10	8975-18	15,000
MVI-12 Adult[b]	50	1199-71	45
MVI-Pediatric[b]	10	1839-31	45

[a]Abbott Laboratories, Chicago, IL.
[b]aaiPharma, Wilmington, DE.

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these products were provided by Abbott Laboratories[a] and aaiPharma.[b] The calculations were based on the maximum aluminum concentration at expiration reported on the label of each product. The desired outcome for patients receiving TPN would be limiting cumulative aluminum exposure to no more than 5 µg/kg/day.

Tables 2 and 3 list the calculated aluminum loads in TPN admixtures prepared from small- and large-volume parenteral nutrient additives prescribed for a given clinical situation. To provide adequate amounts of macro- and micronutrients for both adults and infants, the total aluminum exposure far exceeds the clinical limits set forth in the warning statement required in the package inserts for these commercial products. In admixtures for adults, most of the aluminum content is attributable to the concentration of aluminum in calcium gluconate injection and inorganic phosphates injection. In TPN admixtures for infants, another major source of aluminum is the age-essential amino acid cysteine hydrochloride.

The pharmacist has few options for reducing the aluminum load in TPN formulations. For example, switching to products packaged in plastic vials may result in lower concentrations of aluminum. An example is Sodium Phosphates Injection, USP (Abbott list no. 7391-72), a 10-mL plastic vial, which contains only 180 µg of aluminum per liter, compared with the example listed in Table 1 (Abbott list no. 3295-51), a 50-mL glass vial, which contains 28,000 µg/L. Although the package size makes it inconvenient to prepare TPN admixtures with automated compounding devices, one could meet FDA's clinical limits for aluminum in adults weighing 70–80 kg by switching to the product in the plastic container. However, the other TPN formulations presented in Tables 2 and 3 still do not have a reasonable solution. Therefore, in most

Table 2.
Calculated Aluminum Exposure Associated with Typical Adult Total Parenteral Nutrition (TPN) Admixtures Based on Body Weight[a]

Additive	40 kg	Aluminum (µg)	50 kg	Aluminum (µg)	60 kg	Aluminum (µg)	70 kg	Aluminum (µg)	80 kg	Aluminum (µg)
Aminosyn II (mL)	600	15	750	18.8	900	22.5	1050	26.3	1200	30
Dextrose (mL)	243	6.1	304	7.6	364	9.1	426	10.7	486	12.2
Liposyn III (mL)	100	2.5	125	3.1	150	3.8	175	4.4	200	5
Sterile water for injection (mL)	0	0	0	0	0	0	2.3	0.1	17.3	0.4
Sodium chloride (mL)	10	1	10	1	10	1	10	1	10	1
Sodium phosphates (mL)	10	280	10	280	10	280	10	280	10	280
Sodium acetate (mL)	10	3.6	10	3.6	10	3.6	10	3.6	10	3.6
Potassium chloride (mL)	20	2	20	2	20	2	20	2	20	2
Potassium acetate (mL)	10	2	10	2	10	2	10	2	10	2
Calcium gluconate (mL)	21.5	258	21.5	258	21.5	258	21.5	258	21.5	258
Magnesium sulfate (mL)	2.2	0.6	2.2	0.6	2.2	0.6	2.2	0.6	2.2	0.6
Trace-4 (mL)	3	1.7	3	1.7	3	1.7	3	1.7	3	1.7
MVI-12 (mL)	10	0.5	10	0.5	10	0.5	10	0.5	10	0.5
TPN volume (mL)	1039.7	…	1275.7	…	1510.7	…	1750	…	2000	…
Total aluminum (µg)	…	582	…	587.9	…	593.7	…	599.7	…	606
Aluminum (µg/kg/day)	…	14.3	…	11.6	…	9.8	…	8.4	…	7.5

[a]Nutritional intakes: protein, 1.5 g/kg/day; total energy, ~25 kcal/kg/day (~80% dextrose and ~20% lipid); TPN volume, 25 mL/kg/day; sodium, 100 meq; potassium, 60 meq; calcium, 10 meq; magnesium, 10 meq; phosphorus, 30 mmol.

Table 3.
Calculated Aluminum Exposure in a 100-mL Total Parenteral Nutrition (TPN) Admixture for an Infant[a]

Additive	A_1D_{10}[b]	Aluminum (µg)	A_2D_{10}	Aluminum (µg)	A_3D_{10}	Aluminum (µg)	A_4D_{10}	Aluminum (µg)	A_5D_{10}	Aluminum (µg)
Aminosyn PF (mL)	10	0.3	20	0.5	30	0.8	40	1	50	1.3
Dextrose (mL)	14.2	0.4	14.2	0.4	14.2	0.4	14.2	0.4	14.2	0.4
Liposyn III (mL)	0	0	0	0	0	0	0	0	0	0
Sterile water for injection (mL)	65.2	1.6	54.4	1.4	45.2	1.1	32.4	0.8	21.2	0.5
Sodium chloride (mL)	0	0	0	0	0	0	0	0	0	0
Sodium phosphates (mL)	0.5	14	0.5	14	0.5	14	0.5	14	0.5	14
Sodium acetate (mL)	0	0	0	0	0	0	0	0	0	0
Potassium chloride (mL)	0	0	0	0	0	0	0	0	0	0
Potassium acetate (mL)	0.5	0.1	0.5	0.1	0.5	0.1	0.5	0.1	0.5	0.1
Calcium gluconate (mL)	6.5	78	6.5	78	6.5	78	6.5	78	6.5	78
Magnesium sulfate (mL)	0.1	0.03	0.1	0.03	0.1	0.03	0.1	0.03	0.1	0.03
Trace-4 (mL)	0	0	0	0	0	0	0	0	0	0
Cysteine hydrochloride (mL)	0.8	12	1.6	24	2.4	36	3.6	54	4.8	72
MVI-Pediatric (mL)	2.2	0.1	2.2	0.1	2.2	0.1	2.2	0.1	2.2	0.1
TPN volume (mL)	100	…	100	…	100	…	100	…	100	…
Total aluminum (µg)	…	106.5	…	118.5	…	130.4	…	148.4	…	166.4

[a]Nutritional intakes: amino acids (A) and dextrose (D) are listed as final percentages. Cysteine hydrochloride content is based on 40 mg per gram of protein. TPN volume is calculated on the basis of 100 mL/kg/day in which sodium, 2 meq; potassium, 1 meq; calcium, 3 meq; magnesium, 0.4 meq; phosphorus, 1.5 mmol.
[b]A = final amino acid concentration (percent), D = final dextrose concentration (percent). The subscripts denote the concentration of each ingredient.

clinical cases, there are no "appropriate substitutions if the patient is in the high risk group," as suggested by FDA.[1]

Providing mineral supplementation in TPN formulations on alternate days or reductions in certain nutrient intakes may be considered but would result in some compromise in the effectiveness of TPN therapy. We do not recommend that pharmacists choose alternative electrolyte salts solely to reduce aluminum exposure, especially when this involves calcium and phosphate in TPN admixtures.[5] For example, a change in calcium salts to either acetate or chloride could introduce disastrous consequences if the phosphate content in the same TPN formulation is not reduced accordingly. Parenteral organic phosphate salts may be an alternative, since they, like the organic calcium gluconate salt, have limited dissociation of free interacting ions to form calcium phosphate precipitate in TPN admixtures. This is not possible at present, since parenteral organic phosphate salts are not approved for use in the United States. Hence, efforts to reduce aluminum concentrations in these products should come from improved manufacturing techniques that have existing FDA approval or developing new formulations with low aluminum content.

Finally, certain drug additives can also contribute aluminum, but they do not fall under the proposed agency mandate. In most cases, however, the amounts of aluminum contributed from non-TPN drug products, with the exception of albumin, are very small. Fortunately, the routine use of albumin via TPN admixtures is of questionable clinical value and has been largely abandoned by most clinicians.[6]

A high aluminum content in TPN admixtures is largely the result of three parenteral nutrient additives: calcium gluconate, inorganic phosphates injection (sodium or potassi-

um), and cysteine hydrochloride. Although available products may meet the validation and labeling requirements of the FDA mandate, limiting aluminum exposure from TPN therapy to less than 5 μg/kg/day will not be possible for most patients.

[a]Baker M, Abbott Laboratories. Aluminum values for HPD products used in total parenteral nutrition. Personal communication. 2003 Sep 30.

[b]Currier SJ, aaiPharma. Aluminum values for MVI-12 and MVI-Pediatric. Personal communication. 2003 Oct 6.

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Aluminum exposure through parenteral nutrition formulations: Mathematical versus clinical relevance

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Aluminum exposure from parenteral nutrition (PN) formulations was first associated with osteomalacia some 25 years ago.[1,2] Aluminum contamination in these formulations impaired normal osteoblast proliferation and calcium uptake by bone, thereby contributing to adynamic bone disease. Subsequently, in a study by Bishop et al.,[3] preterm infants (mean age, 29 weeks of gestation) who were administered PN formulations providing a mean ± S.D. of 19 ± 8 μg of aluminum per kilogram per day for approximately 10 days had impaired neurologic development at 18 months of life compared with another group receiving 3 ± 1 μg/kg/day. The concentrations of aluminum in the preterm infants' PN formulations were 250 and 22 μg/L, respectively—the latter being similar to the FDA regulation setting the upper limit for large-volume parenteral injections (e.g., dextrose, amino acids, fat emulsion, sterile water for injection) at 25 μg/L.[4] However, FDA chose not to set a limit for the small-volume parenteral injections such as sodium, potassium, magnesium, calcium, multivitamins, and trace elements solutions used in PN formulations, because a safe lower limit for aluminum content (or maximum) had not been established.[5]

Now the clinical dilemma remains, since most of the aluminum contamination in PN formulations is from the small-volume parenteral injections. The preterm infants who were administered the reduced-aluminum PN formulation in the study by Bishop et al.[3] had the clinical advantage of an organic phosphate source that contains much less aluminum contamination than inorganic phosphates but is not currently available in the United States. Organic phosphate products are compatible when combined with calcium chloride solution, which has a lower aluminum content than calcium gluconate solution. In the United States, calcium chloride is usually not used with inorganic phosphates because of the risk of calcium phosphate precipitation. Instead, calcium gluconate is preferentially used with the inorganic phosphates available, which results in a high aluminum content.

Bishop et al.[3] did not examine patients' serum or urine aluminum concentrations to ascertain if toxicity was a function of either of these, nor did they report aluminum intake from other sources (e.g., colloids, heparin, infant formulas, other medications).[6] Most clinicians would assume that an increased aluminum intake would lead to an increased serum aluminum concentration, but this may be offset by an increase in urinary aluminum excretion.[7] Bishop et al.[3] measured the aluminum concentrations in the phosphate and calcium products (primary sources of aluminum contamination) they used and found 2154 μg/L for potassium acid phosphate solution, 21 μg/L for mixed sodium–potassium

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