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REVIEW

Aluminium in parenteral nutrition: a systematic review

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Aluminium (Al) toxicity problem in parenteral nutrition solutions (PNS) is decades old and is still unresolved. The aim of this review is to gather updated information about this matter, regarding legislation, manifestations, diagnostics and treatment, patient population at risk and the actions to be taken to limit its accumulation. A structured search using MeSH vocabulary and Title/Abstract searches was conducted in PubMed (http://www.pubmed.gov) up to November 2012. Al is ubiquitous, facilitating its potential for exposure. Nevertheless, humans have several mechanisms to prevent significant absorption and to aid its elimination; therefore, the vast majority of the population is not at risk for Al toxicity. However, when protective gastrointestinal mechanisms are bypassed (for example, parenteral fluids), renal function is impaired (for example, adult patients with renal compromise and neonates) or exposure is high (for example, long-term PNS), Al is prone to accumulate in the body, including manifestations such as impaired neurological development, Alzheimer's disease, metabolic bone disease, dyslipemia and even genotoxic activity. A high Al content in PNS is largely the result of three parenteral nutrient additives: calcium gluconate, inorganic phosphates and cysteine hydrochloride. Despite the legislative efforts, some factors make difficult to comply with the rule and, therefore, to limit the Al toxicity. Unfortunately, manufacturers have not universally changed their processes to obtain a lower Al content of parenteral drug products (PDP). In addition, the imprecise information provided by PDP labels and the high lot-to-lot variation make the prediction of Al content rather inaccurate.

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INTRODUCTION

Aluminium (Al) toxicity in parenteral nutrition solutions (PNS) has been a problem for decades and is still unresolved. Europe lacks a global legislation about the upper limit for Al contamination. In the United States, in an effort to limit patients' exposure to Al and to prevent cases of Al toxicity, the American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) Working Group on standards for Al content in PNS established in 1991 a series of thresholds (upper *safe* limit, *unsafe* limit, and *toxic* limit) for Al intake for patients on long-term PNS.

The United States Food and Drug Administration (FDA) endocrinologic and metabolic drugs advisory panel, in 2004, and after several deferrals, issued a rule governing Al content in large volume parenterals (LVPs) and small volume parenterals (SVPs) used to prepare PNS.

Because this regulation applies to industry only, ASPEN issued a statement in 2010 on Al in PNS that provides some guidance to clinicians.

Despite the legislative efforts, some factors have made difficult to comply with the rules and, therefore, to limit the Al toxicity. In this article, we describe how much has been done to limit the Al content in PNS, and highlight its importance and the actions that should be taken to limit it.

MATERIALS AND METHODS

A structured search using MeSH vocabulary and Title/Abstract searches was conducted in PubMed (http://www.pubmed.gov) up to November 2012. The language of the publications was restricted to English. The terms used were as follows: (((aluminium(Title/Abstract)) or aluminium (Title/Abstract)) and parenteral nutrition (Title/Abstract), rendering 107 publications. Six were excluded according to language criteria, resulting in 101 articles. References from these articles chosen were browsed, yielding an additional 30 papers for potential consideration.

FINDINGS

Al characteristics

Al is the lightest, least dense and third most abundant mineral within the earth's crust (8% by weight) after oxygen and silicon.[1–8] It has no known functions in the human body, although a significant role in biomolecular compaction has been proposed.[5,9] Its wide distribution clearly facilitates the potential for human exposure, which occurs through air, food and water, but it is also present in medical, cosmetic and environmental products.[6,9] Of these, PNS stand out as a substantial source of this toxic metal, as many parenteral drug products (PDP) used to compound them contain Al as a contaminant or as a component of the raw materials.[9,10]

It is estimated that humans ingest between 3 and 20 mg of Al per day.[1,9] Food and beverages provide 2.5–13 mg of Al daily, whereas drinking water may account for 0.2–0.4 mg per day. Drugs such as antacids can contribute up to 500 mg.[6] However, despite this intake, it will not accumulate in the body. Humans have several mechanisms to prevent significant absorption of Al and to aid its elimination; therefore, the vast majority of the population is not at risk for Al toxicity from oral or enteral intake.[9] In healthy people, both the lungs and the skin are very effective at reducing Al absorption, as is the gastrointestinal tract, which

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typically allows <1% of ingested Al into the blood stream.[1,9,11,12] Ninety nine per cent of absorbed Al is lost in the urine and a minor portion being cleared in the bile. Thus, the renal excretion is the primarily via of elimination.[1,2,12,13]

However, when protective gastrointestinal mechanisms are bypassed (for example, parenteral fluids), renal function is impaired (for example, adult patients with renal compromise and neonates) or exposure is high (for example, long-term PNS), Al is prone to accumulate in the body, notably in bone, liver and central nervous system, and also in the spleen, kidneys and other tissues.[1,14] PNS are then one of the parenteral fluids that pose greatest risk for Al accumulation owing to their Al content and their administration directly into the circulation bypassing the gastrointestinal tract.[12]

Al in PDP

Al is present in all the PDP used to elaborate PNS. Furthermore, product manipulation, containers and administration sets add Al to the mixture.[10,15] Al contamination of PNS has been recognised since the 1980s, although it was higher than it is at present.[9] Previous studies from the 1980s estimated daily intakes of Al from 80 to 100 μg/kg/day, which is almost 50-fold more than the present mean intake. This change is a function of reduced contamination of PNS through its additives.[16]

A high Al content in PNS is largely the result of three PDP: calcium gluconate (CaGluc; up to 81%), inorganic phosphates (especially potassium) and cysteine hydrochloride.[4,8,10,12,17–20]

Historically, replacement of casein hydrolysate with crystalline amino acids, which are very low in Al, substantially reduced the Al load 50–100 times in adult patients receiving PNS. This protein source is no longer available, and thus may no longer be considered a source of Al toxicity.[1,14,16,21] Currently, there are other changes that may lead to Al reduction:

Calcium and phosphorus are prescribed in small amounts but are relevant, as both are important sources of Al and have the potential for developing calcium phosphate precipitates. CaGluc is commonly used in PNS and has replaced calcium chloride (CaCl), because the risk of precipitation with phosphate is lower.[17,22] However, PNS made with CaCl contain significantly less Al compared with those made with CaGluc.[17,23] Another strategy to reduce the risk of calcium phosphate precipitation is to use an organic source of phosphorus, more compatible with CaCl than the inorganic phosphates.[2,3,10] However, although widely used in Europe, they are unavailable in many countries including the United States and Canada. Furthermore, although inorganic phosphates are considered as high Al-content products, potassium phosphate (KPho) usually renders more Al to PNS than sodium phosphate. Therefore, using a sodium or a mixed sodium–KPho solution rather than the potassium salt would significantly reduce Al exposure through PNS.[3,24] Another issue is the under-mineralisation of bone in low-birth-weight infants receiving PNS partly because of the delivery of insufficient amounts of calcium and phosphorus, limited by the low solubility of calcium phosphate. A possible alternative is calcium glycerophosphate, which has confirmed as effective regarding mineral retention as equimolar intakes of calcium and phosphorus from CaGluc and KPho respectively. Also, and higher concentrations of these minerals can be kept in solution when they are provided as calcium glycerophosphate.[25–27]

The amount of Al leached from glass containers with rubber closures is also a significant contributor of Al.[10] For instance, repackaging CaGluc from glass containers to polyethylene vials reduces the mean Al concentration from 5000 to 195 μg/l (a 96% decrease).[3,10,12] PDP should be stored in containers that do not interact physically or chemically with the preparations. This high chemical resistance is, however, obtained by the addition of mainly boric and Al oxides to glass, consequently turning glass into a source of Al.[28] Low pH favours exchange of metal ions from glass, whereas high-pH solutions promote the dissolution of the glass surface itself.[29] Solutions such as CaGluc, sodium phosphate and sodium acetate form complex anions that dissolve Al from the glass containers during autoclaving.[2,12,24] (Table 1). Table 2 shows the content of Al measured in different PNP as published in several recent studies. Table 3 lists some relevant products currently marketed for PNS preparations in Europe.

Patient population at risk

As the kidneys are the major route of Al elimination, the patients at greatest risk of accumulation receiving PNS are those with renal compromise and infants with immature renal function, although other patients who receive these Al-contaminated parenterals are also at risk for Al loading.[10,12,14] (Table 4).

- During pregnancy, the foetus is susceptible to Al contamination, as it is transferred transplacentally. Al does not appear to transfer into breast milk in any appreciable. In animal models, less than 2% of a daily dose reached breast milk.[1,13]
- In premature infants, toxicity appears to be negatively correlated with gestational age. In addition to possessing immature renal function, they are more prone to Al toxicity because of their increased calcium and phosphorus requirements, thus exposing them to more contaminants from parenterals that contain these minerals.[1,16] Even intakes of <2 μg/kg/day, the level suggested by the ASCN/ASPEN as being safe, may be toxic in this population.[1] Healthy neonates may be able to handle more Al; however, there are no such studies available upon which we could safely estimate acceptable upper levels of Al from parenteral or injectable sources in healthy children.[11]
- In adults, age represents a risk factor for kidney function impairment, as during normal aging humans lose up to 50% of their glomeruli between 40 and 85 years of age.[11] Elderly patients may also be at a similar risk of Al-related toxicity. However, a study reveals that most patients with acute kidney injury who require PNS do not receive excessive exposure to Al. This was due, in part, to the fact that patients with better renal function received more calcium and smaller doses of phosphorus. Patients with the worst renal function were more apt to have hyperphosphatemia and would therefore receive PNS without phosphorus.[8]
- In geriatric patients, Al absorption becomes more efficient with advancing age; toxicity may not be as dependent on renal function owing to a weakened gastrointestinal protective barrier.[1]
- Other populations at risk for Al toxicity are burn patients who have received large amounts of albumin to maintain oncotic pressure, and plasmapheresis patients who have been given large amounts of albumin.[1]

Al toxicity manifestations

Reports of Al toxicity from PNS have been cited in the medical literature for several decades.[2,12] Unfortunately, the published literature is primarily limited to studies published in the 1980s and 1990s, and the majority of the literature supporting the need to minimise Al exposure in the PNS-dependent patient is more than 30 years old.[13] Recent publications refer back to these classic papers, and the actual prevalence of Al toxicity in the parenteral nutrition-dependent patients still remains to be unknown and difficult to calculate, as published evidence consists mainly of case reports or small studies.[1]

Signs and symptoms of increased tissue Al levels include possibly neurodegenerative disorders such as dialysis encephalopathy, progressive dementia, impaired neurological development,

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Table 1. Grading quality of evidence

Study/ date	*Purpose*	*Quality assessment*					*Summary of findings*			
		Design	*Quality*	*Consistency*	*Directness*	*Other modifying factors*	*Sample size*	*Effect*	*Quality*	*Importance*
Aluminium in parenteral drug products										
Poole 2011([45])	Determine the least Al-contaminated products to be used when compounding PNS	Observational study	No serious limitations	No important inconsistency	Direct	All products from all manufacturers available in the United States were tested.	Three lots of 16 PNS components	Measured Al concentrations were significantly lower than the labelled concentration. ($P<0.05$) Calcium gluconate, potassium phosphate and sodium phosphate contained the higher Al concentration.	High	Critical
Bohrer 2001([28])	To determine the influence of glass packing on the contamination of products by Al	Observational study	No serious limitations	No important inconsistency	Direct	Strong association	19 amino acid solutions stored in glass type II flask and Al measured at different intervals.	Cysteine (A), cystine (B), aspartic (C) and glutamic acid (D) became contaminated by Al. Measures μg/Al g aa/l) at 15.30 and 60 days: A: 230; 725; 1056. B: 458; 1661; 3026. C: 35; 75; 106. D: 27; 68; 87.	High	Critical
Driscoll 2005([19])	To determine the most contaminated components of PNS	Observational study	Limitations[a, b]	No important inconsistency	Direct	None	16 products	Sodium phosphate, cysteine hydrochloride and Calcium gluconate were the most Al-contaminated componentes	Moderate	Critical
Draper 1991([25])	CaGP vs CaGluc and KPho in PNS for Ca and P retention	Clinical trial	Serious limitations[c]	No important inconsistency	Study in piglets	None	10 CaGP ($n=5$) CaGluc & KPho ($n=5$)	Ca and P retention (mean ± s.e.m.) From CaGP to CaGluc and KPho 14.5 ± 0.2 vs 2.2 ± 0.3 mmol Ca/kg/day ($P<0.01$) 13.3 ± 0.4 vs 2.4 ± 0.1 mmol P/kg/day ($P<0.01$)	Low	Critical
Hanning 1991([26])	Efficacy of CaGP vs CaGluc + KPho on mineral retention	Clinical trial	No serious limitations	No important inconsistency	Direct	Equimolar intakes of Ca and P	16 CaGP ($n=6$) CaGluc + KPho ($n=9$)	Ca and P retention (mean ± s.d.) From CaGluc and KPho to CaGP 1.2 ± 0.2 vs 1.0 ± 0.2mmol Ca/kg/day 1.1 ± 0.3 vs 0.8 ± 0.3 mmol P/kg/day	High	Critical
Koo 1986([20])	Sources of Al in PNS	Observational study	No serious limitations	No important inconsistency	Direct	Great variety of manufacturers and samples. Samples measured	123 samples from 16 different PN components	Calcium gluconate, sodium phosphate and potassium phosphate, by this order, were the most heavily contaminated	High	Critical
Aluminium toxicity manifestations										
Fewtrell 2009[24]	To test the hypothesis that neonatal Al exposure also adversely affects long-term bone health	Clinical trial	No serious limitations	No important inconsistency	Direct	The median exposure of 55μg/kg/day of Al as a significant threshold is well above the mean Al exposure from s.d. PNS and the FDA recommendations	59 patients (mean Al exposure) S: standard-Al PNS [21.3μg/kg/day)($n=26$) AD: Al-depleted PNS (3 μg/kg/day) ($n=33$)	The total Al exposure from PNS as a continuous variable failed to be a significant predictor of adjusted BMC at any site. Patients on intakes over 55μg/kg/day had lower hip BMC by 7.6% (95% CI: 0.12 -13,8) than intakes under that threshold $P=0.02$	Moderate	Critical
Bishop 1997([31])	To investigate the effect of perinatal exposure to intravenous Al on the neurologic development of infants born prematurely	Clinical trial	No serious limitations	No important inconsistency	Direct	Very strong association	182 premature infants (mean Al exposure of 180 ml/kg/day of PNS) S: standard-Al PNS [45 μg/kg/day)($n=26$) AD: Al-depleted PNS (4-5 μg/kg/day) ($n=$)	For patients on S with no neuromotor impairment, increasing Al exposure was associated with a reduction in the mental development index ($P=0.03$) with an adjusted loss of one point per day of intravenous feeding.	High	Critical

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Table 1. (Continued)

Study/ date	Purpose	Quality assessment					Summary of findings			
		Design	*Quality*	*Consistency*	*Directness*	*Other modifying factors*	*Sample size*	*Effect*	*Quality*	*Importance*
Estimating aluminium loading										
Migaki 2012([17])	Calculated vs measured Al concentrations in PNS containing CaCl + NaPhos vs CaGluc & KPho	Observational study	Limitations[a]	No important inconsistency	Direct	Strong association in B and C	12 PNS samples (4 each) CaCl + NaPhos (A) CaGluc + NaPhos(B) CaGluc + KPhos(C)	Measured vs calculated Al concentration (μg/dl) A: 6 vs 6.3 B: 22.9 vs 54.9 C: 31.5 vs 73.3	Moderate	Critical
Poole 2010([12])	To compare calculated vs measured Al contamination in PNS and ascertain wether the actual Al exposure exceeds the FDA recommendations	Observational study	No serious limitations	No important inconsistency	Direct	Very strong association	40 neonatal PNS	The calculated Al contamination was twice as much as the actual measured Al content Calculated 5–10 times the FDA limit Measured: 3–5 times the FDA limit	High	Critical
Poole 2008([2])	To determine patient's daily Al load delivered from PNS	Observational study	Limitations[b]	No important inconsistency	Direct	Products used with the lowest content available	13 384 PNS	Calculated average Al exposure is 23.14 μg/kg/day. Meeting the FDA recommendations only possible on patients weighing > 50 kg.	Moderate	Critical
Brown 2008([8])	To determine the potential for Al toxicity caused by PNS in acute kidney injury adults	Observational study	Limitations[b]	No important inconsistency	Direct: adults with acute renal injury (sCr ≥ 1.5 times that of admission)	None	36 PNS	29/36 had safe calculated aluminium exposure (< 5 μg/kg/day)	Moderate	Critical
Driscoll 2005([19])	Calculating Al content in PNS	Observational study	Limitations[a, b]	No important inconsistency	Direct	None	5 typical adult PNS of 40–80 kg	40 kg: 14.3 μg/kg/d 50 kg: 11.6 μg/kg/day 60 kg: 9.8 μg/kg/day 70 kg: 8.4 μg/kg/day 80 kg: μg/kg/day.	Moderate	Critical
Advenier 2003([16])	To determine the Al contamination of children on long-term PNS	Observational study	No serious limitations	No important inconsistency	Direct	None	10 children	Mean Al daily intake 2.16 ± 0.81 μg/kg/day	Moderate	Critical
Deferoxamine therapy										
Kan 2010([34])	Efficacy of standard vs low dose of DFO in haemodialysis and serum Al 20 μg/l participants.	Clinical trial	No serious limitations	No important inconsistency	Direct	None	42 Low-dose group: 2.5 mg/kg/week ($n = 21$) Standard dose: 5 mg/kg/week ($n = 21$)	Successful treatment response (sAl rise < 50 μg/l after DFO test) Low dose: 62%vs standard dose 57% ($P = 0.75$)	High	Critical

Abbreviations: AD, Alzheimer's disease; Al, aluminium; BMC, bone mineral content; CaGP, calcium glycerophosphate; CaGluc, calcium gluconate; CI, confidence intervals; DFO, deferoxamine; FDA, Food and Drug Administration; KPho, potassium phosphate; PNS, parenteral nutrition solution; sCr: serum creatinine. **Quality:High** = Further research is very unlikely to change our confidence in the estimate of effect. **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. [a]Only one manufaturer tested. [b]Calculation of Al concentration through the quantity expressed on the label tends to overestimate the intoxication. [c]CaGP was in a concentration that provided 3.6 and 7.1 as much calcium and phosphorus, respectively, to the PNS than CaGP and Kphos, as its solubility its better solubility allow higher concentrations. [d]The Al intake from PNS was not measured through the actual PNS but its components.

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Table 2. Aluminium measured in different parenteral nutrition products according to recent published studies

Aluminium μg/l	*Migaki et al JPEN 2012 (ref.[16])*	*Poole et al. JPPT 2011 (ref.[45])*	*Fewtrell et al. PNS 2011 (ref.[15])*	*Poole et al. JPGN 2010 (ref.[12])*	*Oliveira et al. JPEN 2010 (ref.[46])*	*Brown et al. 2008 (ref.[8])*
Sterile water	25[a]	<5[b], 5[c], 6.6[a], <5[d], <5[e]	—	<5[e]	3.8[f]	<1[e]
Amino acids solutions	25[d]	7[d]	30[g]	<5[d]	90.1[g], 124[e]	3.1[e], 5.9[e]
Dextrose	25[a]	20[d], 14[a]		7[a]	19.2[h], 17.3[e], 13.5[e], 4.6[g], 17.2[g], 23[f], 20.5[i]	12.5[e]
Lipid emulsions		11[g]	2[g]	15[g]	19.7[g], 112.6[g]	1.3[g]
Sodium glicerophosphate					263.7[g]	
Calcium gluconate	9400[b]	2487[b], 2812[c]	776[j]	3234[c]	9205[k], 19400[k]	278[b]
Potassium phosphate	37000[a]		56[j]	8280[c]		223[b]
Sodium phosphate	180[a]			622[b]		
Potassium acetate				42[a]		
Sodium acetate	200[a]			83[a]		
Calcium chloride	1000[a]		10[j]			
Potassium chloride	100[a]			<5[a]	62[l]	
Sodium chloride				<5[a]	2.9[f], 1.6[l], 62.5[i]	57[a]
Zinc chloride				41[a]		
Magnesium sulphate	300[c]	165[b], 109[c], 122[a]		14[a]	63.1[l], 87.3[f]	
Selenium	2500[b]			87[b]		
Trace elements						
Paediatric trace elements				414[b]		
Multi-trace elements					1049[m], 2065[m], 1663[m]	15[b]
Vitamins preparations	6250[b], 30[e]		6[g], <2[g], 24[n]	14[e]	549[o], 112.1[p], 1509[p]	
Cysteina						
Chromium						25[a]
Copper						10[a]

Abbreviation: JPEN, Journal of Parenteral and Enteral Nutrition; JPGN, Journal of Pediatric Gastroenterology and Nutrition; JPPT, The Journal of Pediatric Pharmacology and Therapeutics; PNS, Proceedings of the Nutrition Society. **Manufacturer:** [a]Hospira. [b]American Regent. [c]APP pharmaceuticals. [d]B. Braun Medical. [e]Baxter. [f]Halex Istar. [g]Fresenius Kabi. [h]Aster. [i]Isofarma. [j]Not specified [k]Hypofarma. [l]Equipex. [m]Darrow. [n]In-house preparation. [o]Cristália. [p]Farmalab.

Table 3. Relevant products currently marketed for parenteral nutrition solutions preparations in Europe

Brand name	*Manufacturer*
Amino acid solutions	
Aminofusin	Baxter
Aminopaed	Fresenius Kabi
Aminoplasmal	B. Braun
Aminosteril	Fresenius Kabi
Aminoven	Fresenius Kabi
Glamin	Fresenius Kabi
Nephrotect	Fresenius Kabi
Primene	Fresenius Kabi
Tauramin	Grifols
Throphamine	b. Braun
Travasol	Baxter
Synthamin	Baxter
Vamin	Fresenius Kabi
Vaminolact	Fresenius Kabi
Lipid emulsions	
ClinOleic	Baxter
Intralipid	Fresenius Kabi
Ivelip	Baxter
Lipofundin	B. Braun
Lipoplus	B. Braun
Lipovenos	Fresenius Kabi
Omegaven	Fresenius Kabi
Smoflipid	Fresenius Kabi
Soyacal	Grifols
Structolipid	Fresenius Kabi
Vitamins preparations	
Cernevit	Baxter
Soluvit	Fresenius Kabi
Vitalipid	Fresenius Kabi
Trace elements	
Addamel	Fresenius Kabi
Decan	Baxter
Peditrace	Fresenius Kabi

Table 4. Patient population at risk of Al accumulation

Patient population at risk	*Causes*
Renal compromise	Kidneys are the major route of Al elimination
Foetus	During pregnancy Al is transferred transplacentally
Premature infants	Al toxicity negatively correlated with gestational age: immature renal function, increased calcium and phosphorus requirements
Elderly patients	Weakened GI protective barrier Normal renal function deterioration
Burn patients	Al-contaminated albumin to maintain oncotic pressure

Abbreviations: Al, aluminium, GI, gastrointestinal.

Alzheimer's disease (AD) and Parkinson's disease, as well as metabolic bone disease including impaired bone growth, bone pain, proximal muscle weakness, multiple nonhealing fractures, premature osteoporosis, osteopenia and osteomalacia. Microcytic anaemia and cholestasis have been described as well.[1,2,4,6,11,12,30] (Table 1).

Impaired neurological development

A key study by Bishop *et al.*[31] that contributed to the FDA rule governing Al contamination compared neurological development in premature infants who received a standard PNS formula (median: 45 μg/kg/day of Al) or an Al-depleted formula (median: 4–5 μg/kg/day of Al) for a period of 5–16 days. The authors estimated that for infants receiving the standard PNS, the expected reduction in the Bayley Mental Development Index score would be 1 point per day of intravenous feeding.[12]

Alzheimer disease

Al has a direct and active access to the brain, where it accumulates in a region-specific manner that highly implicates its involvement

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Table 5. Thresholds for aluminium delivered by parenterales and plasma levels

	Safe dose/level	*Unsafe dose/level*	*Toxic dose/level*	*Large volume parenterals*	*Small volume parenterals*
ASCN/ASPEN	≈2 μg/kg/day	≈15–30 μg/kg/day	≈60 μg/kg/day	—	—
FDA	⩽5 μg/kg/day	>5 μg/kg/day	—	⩽25 μg/l	Not established
K/DOQI	<50 μg/l[a]	50–300 μg/l[a]	>300 μg/l[a]	—	—

Abbreviations: ASCN, American Society for Clinical Nutrition; ASPEN, American Society for Parenteral and Enteral Nutrition; FDA, Food and Drug Administration; K/DOQI, Kidney Disease Outcomes Quality Initiative. [a]After deferoxamine test.

in AD. Experimental data clearly show that all neurophysiological parameters required for AD are efficiently targeted for impairment by Al.[11]

Metabolic bone disease

Metabolic bone disease is a well-known complication of prolonged PNS use due to Al toxicity.[1,10,24] Although their exact incidence has not yet been established with certainty, percentages range from 30%–40% to 100% in various case reports.[21]

The clinical picture of bone involvement is variable. In the majority of cases, patients are asymptomatic, whereas in others they may manifest bone pain or fractures for minimal traumas, which are typically vertebral fractures. The finding of a reduced bone mineral density is common, although not dissimilar to that observed in the control groups, and is likely sustained mostly by the metabolic consequences of the underlying disease.[21] In infants, the development of metabolic bone disease can occur more quickly.[1] Neonates who are exposed to parenteral Al may have reduced lumbar spine and hip bone mass during adolescence, which are potential risk factors for later osteoporosis and hip fracture.[24]

The candidate mechanisms for Al toxicity include suppression of parathyroid hormone secretion[14,21] and Al accumulation primarily in bone , which reduces bone formation thereby contributing to adynamic bone disease.[3,14,24] Finally, Al-like lead is thought to have either a primary or secondary suppressive effect on the renal enzyme 25-hydroxyvitamin D-1α hydroxylase. This enzyme converts circulating 25-hydroxyvitamin D into 1, 25-dihydroxyvitamin D at the level of the renal tubule. The latter metabolite is the corticosteroid hormone form of the vitamin and exerts maximum biological activity.[14,21]

Hepatotoxicity

Very little is known about the hepatotoxic effects of Al in either animals or humans. The mechanism of Al toxicity is far from clear understanding, but it is suggested that Al generates reactive oxygen species (ROS) that cause lipid peroxidation and oxidative damage to proteins and DNA. In addition, Al caused hepatic haemorrhage, cellular degeneration and necrosis of hepatocytes.[30]

Animal models definitely indicate an effect of Al on bile metabolism, although there has never been any proven relationship between hepatic Al content in humans and degree of cholestasis.[14]

Dyslipemia

Al toxicity, along with oxidative stress (H_2O_2), has been associated with lower levels of L-carnitine, diminished β-oxidation and increased lipid accumulation in human astrocytes and hepatocytes compared with the controls. L-carnitine is an amino acid derivative indispensable for the metabolism of lipids. Its synthesis is a multistep enzymatic process that necessitates the participation of lysine, methionine and α-ketoglutarate (KG). Exposure of the Al- and H_2O_2-treated cells to α-KG led to the recovery of L-carnitine production with the concomitant reduction in ROS levels. It appears that the channelling of KG to combat oxidative stress results in decreased L-carnitine synthesis, an event that contributes to the dyslipidemia observed during Al and H_2O_2 insults in these mammalian cells. Hence, KG may help alleviate pathological conditions induced by oxidative stress.[32]

Genotoxic activity

There are only a few studies in the literature about the genotoxic activities of Al. However, it has been found that Al induces chromosomal aberrations and DNA damage.[6]

DIAGNOSTICS AND TREATMENT

The widely used analytical technique for the direct detection of the Al in biological fluids is the graphite furnace atomic absorption spectrometry,[7] although blood levels continue to be a poor predictor of the presence or absence of Al toxicity. Similarly, urine concentrations have also been used, but the relationship of these levels to disease severity has not been clearly established.[1] On the other hand, although an increased Al intake does not necessarily lead to an increased serum Al concentration, as this may be offset by an increase in urinary Al excretion, its high value should alert of a risk of toxicity.[3,16] The deferoxamine (DFO) infusion test has been used to determine the total Al load. DFO is a chelating agent that removes Al from tissue stores and allows for more accurate serum levels (see below).[1] However, the lack of standardised testing makes the diagnosis of Al toxicity difficult. A thorough medical history and evaluation of clinical signs and symptoms in conjunction with laboratory tests and imaging studies are necessary in order to make an accurate diagnosis.[13]

Treatment options in the management of Al toxicity continue to be limited. Some agents have been proposed, although DFO is the most widely used substance. However, reduction or elimination of Al-rich components continues to be the most effective means of management.[1,13]

Taurine

The toxic effects of Al may be mitigated by taurine through the improvement of the cellular antioxidant defence system, stabilisation of cell membrane, and prevention of lipid peroxidation. It also seems to have direct beneficial effects on liver parenchymal cells. The chemical similarity of taurine to acetylcysteine, an agent used to treat heavy metal-induced toxicity, and the fact that cysteine is a precursor of taurine, is an encouraging factor to use taurine against metal-induced hepatotoxicity.[30]

α-ketoglutarate

Exposure of the Al- and H_2O_2-treated cells to KG led to the recovery of L-carnitine production, with the concomitant reduction in ROS levels, reducing lipid accumulation.[32]

Iron

The potential for complications of Al exposure is closely related to the patient's iron status. The iron transport protein transferrin serves as the primary Al-binding ligand, accounting for as much as

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90% of all binding. Moreover, when iron is bound to transferrin, the overall affinity of transferrin for Al is reduced.[13]

Deferoxamine

DFO chelation therapy has been used to treat PNS-associated Al toxicity. In 2003, the Kidney Disease Outcomes Quality Initiative recommended a DFO test if there are elevated serum Al levels (60–200 μg/l) or clinical signs and symptoms of Al toxicity. If Al levels are >200 μg/l, DFO test should be delayed until intensive dialysis reduces Al below that threshold to avoid DFO-induced neurotoxicity. The test is considered positive if the increment of serum Al is >50 μg/l over the serum Al level previous to DFO test, and a different management is proposed according to that level (*algorithm 1*).[33] The recommended dose of DFO is 5 mg/kg, both treatment (weekly) and test, although an article of Wei-Chih K. *et al.* concluded that low-dose DFO (2.5 mg/kg/s.e.m.) may offer similar therapeutic effects.[33,34] (Table 1).

Despite its use, DFO has its own risks:

- Refractory hypocalcaemia: in one case report, when an infant was treated with DFO for Al toxicity, the urinary Al excretion increased several-fold 24 h after each dose; however, the patient developed mild hyperparathyroidism rendering refractory hypocalcaemia despite receiving continuous infusions of calcium.[1,14] As urinary calcium excretion was negligible, a likely explanation would be that Al was chelated from bone, and the low serum calcium would be deposition in the patient's demineralised bone, the chief repository of body calcium.[35]
- Others side effects include Dementia, acute Al neurotoxicity and fatal mucormycosis.[36–40]

Regulations

In an effort to limit patients' exposure to Al and to prevent cases of Al toxicity, the ASCN/ASPEN working Group on standards for Al content in PNS established in 1991 a series of thresholds for Al intake for patients on long-term PN (Table 5). A 'safe' dose does not result in the accumulation of Al in tissues or fluids and is associated with unknown toxic effects. An 'unsafe' dose is the amount that results in tissue loading, but no documented toxicity. A 'toxic' dose is one that results in tissue accumulation and symptoms of toxicity.[41]

The FDA endocrinological and metabolic drugs advisory panel, in 1986, recommended that Al be eliminated from ingredients used in the compounding of PNS. In January 2000, the FDA amended its Regulations on Al in LVPs and SVPs used in total parenteral nutrition with the Final Rule, whose implementation was delayed several times to allow pharmaceutical manufacturers time to comply and was finally put into effect from July 2004.[12,42,43] This federal regulation would require that:

- The Al content of all LVPs used in PNS therapy not exceed 25 μg/l, and that this statement be on the package insert.
- For SVPs, the maximum level of Al at expiry be stated on the immediate container label.
- All products used in PNS therapy contain a warning statement about Al toxicity in patients with impaired kidney function and in neonates receiving PNS therapy, and that levels of Al at greater than 4–5 μg/kg/day in these patients are associated with central nervous system and bone toxicity.
- Applicants and manufacturers develop validated assays methods to determine the Al content in PDP.

Because this regulation applies to industry only, A.S.P.E.N., in 2010, issued a statement on Al in PNS that provides some guidance to clinicians.[9, 10]

DISCUSSION

Al toxicity problem in PNS is decades old, and still unresolved. As the protective gastrointestinal tract is bypassed with PNS administration, Al accumulation is practically fully dependent on the renal function. In patients in whom this excretion via is impaired, or in long-term treatment, Al will inevitably accumulate.

The issue echoed the FDA that, in an effort to limit patients' exposure to Al and to prevent cases of Al toxicity, required manufacturers to limit and/or state the quantity of Al their products contained and validate assays methods to determine it. The aim of the FDA was to bring the attention of manufacturers and healthcare providers, and put a limit to an old problem that had been around for decades. The rule was finally implemented in 2004, and even nowadays some problems threaten its main purpose:

Estimating Al loading

Labelling. Although not explicitly stated in the FDA regulations, pharmacists are expected to calculate the maximal amount of Al contained in a patient's PNS. However, calculating Al content in PNS using labelled concentrations presents several problems:

- LVPs only state that they do not contain more than 25 μg/l, but fail to specifiy an accurate quantity. Using labelled concentrations that will not be exceeded at the product's expiry does not allow to accurately determine the patient's actual exposure to Al.
- For SVPs, a safe lower limit for Al content (or maximum) had not been established, although a specific concentration at the expiry of the product must be stated.
- Neither all ingredients used in PNS nor products marketed outside the US are required to meet the stipulations of the FDA mandate. Commonly used PN additives such as albumin, famotidine, heparin, ranitidine and insulin are not required to meet the current labelling standards for Al content.

Products intra and intervariability. Al contamination has been found to vary significantly between types of components, between manufacturers and between component lots from the same manufacturer, which suggests lack of quality control.

Measured versus calculated. Many studies show that the measured daily Al exposure is actually significantly less than that calculated from manufacturers' labels, as the label shows the content of Al at the end of the expiry date; thus, the potential for overestimation of Al content exists.[2,10,12,14,16,18,44–46] (Table 1).

FDA guidance

Difficulties encountered in meeting FDA recommendations. Many studies agree in the inability to meet FDA guidelines of <5 μg/kg/day using current PDP to compound PNS. It is virtually impossible, both measuring or calculating the Al content, to prepare a PNS that meets the nutritional needs of the patient, as providing adequate amounts of macronutrients and micronutrients for both adults and infants. The total Al exposure far exceeds the clinical limits set forth in the warning statement required.[3,4,10,12,19,24] Previous studies of Al exposure from PNS had reported Al intakes in the range of 10–60 μg/kg/day. Even other studies using the products with the least amount of labelled Al content to prepare PNS could not meet the FDA-recommended safe amount.[2] Poole *et al.* concluded that meeting the recommendation is only possible in patients weighing >50 kg by using currently available PDP, and calculated the Al exposure in infants >3 kg to be 30 to 60 μg/kg per day.[2,24] In infants, the inability to meet the FDA guidelines is most likely due to the higher need for

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calcium and phosphate compared with adults.[12] Calcium and phosphorus intakes would need to be eliminated or substantially decreased in order to limit the Al load presented by PN.[10] Furthermore, according to the latest vaccination schedule, every child in the US will receive a total of 5–6 mg of Al by the age of 2 years, or up to 1.475 mg of Al during a single visit to the paediatrician.[11]

Accuracy of the FDA recommendations. It appears that most patients receiving PNS have an elevated serum Al level despite normal renal function, even when the measured Al intake is less than the FDA recommendation of 4–5 μg/kg/day. Clinicians should be aware of the implications associated with metabolic bone disease; however, the neurologic complications associated with Al may be evident only for premature infants and not at the time of the infusion, but several months later.[3]

Low-Al product options

Unfortunately, there are very few low-Al products available.[3,19,47,48] Industry has not yet universally embraced the Al problem. For instance, only very few manufacturers have currently repackaged CaGluc salts into plastic containers.[1] New methods for removal of Al from calcium salts have been developed but have not been put into use. In countries in which such alternatives are readily available, their utilisation is recommended.[1] In addition, the different current markets make, for example, that the organic phosphorus products be allowed in Europe but unavailable in the United States. These facts render a shortage of low-Al-content PSP alternatives that threaten the FDA recommendation.

Recommendations

Reducing Al contamination is a shared task between manufacturers and healthcare providers involved in the provision of PNS:

- The need for changes in the manufacturing process for PNS components is essential. Manufacturers should improve manufacturing techniques, approved by FDA, in order to provide a wide range of low-Al-content PNS alternatives that make it feasible to meet the requirements.
- Ideally, and given the difficulties and overestimation encountered when estimating the Al loading using labelled concentrations, Al content of every PNS should be measured.
- All healthcare providers should ensure that ingredients with the lowest amount of Al are used in the preparation of PNS. While providing adequate and safe amounts of macronutrients and micronutrients, pharmacists should identify manufacturers whose products result in less Al contamination than those of others. By choosing products with the least amount of Al contamination, Al exposure and the potential for Al toxicity can be reduced. However, selection of alternative electrolyte salts is not always recommended solely to reduce Al exposure, especially when this involves calcium and phosphate, owing to the their high capacity of precipitation. For example, a change in calcium salts to either acetate or chloride could introduce disastrous consequences if the phosphate content in the same PNS formulation is not reduced accordingly.[49]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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