Aluminum Toxicity: Issues and Insights

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The following special report is based on information presented at an Aluminum Toxicology Experts Meeting held on July 1, 2003, in Dallas, Texas.

Toxic levels of aluminum may increase morbidity and mortality of select patients, especially those with chronic renal failure.[1,2] To update the medical community about the current status of aluminum toxicity, participants reviewed human exposure to aluminum, medical toxicity of aluminum, specific patients at risk, and regulatory considerations.

The information presented in this report reflects the goals established for the Aluminum Toxicology Experts Meeting:

- *Increase awareness of the dangers of aluminum toxicity in certain patient populations*
- *Promote safe levels of aluminum content in all medical products*

Overview

As the third most common element in the Earth's crust, aluminum (Al) is one of the most abundant metals in the environment.[2,3] Air and drinking water are common sources of Al exposure. In addition, this prevalent metal is found in various over-the-counter (OTC) and prescription medications, food, and food containers.

People are continuously exposed to Al by ingesting water, food, and dust particles.[2] Estimates suggest that adults consume approximately 3 to 5 mg of Al in their daily diet. Healthy individuals can easily handle normal Al intake, since absorption in the gastrointestinal (GI) tract is low.[4] The GI tract provides efficient protection against Al absorption, and it is estimated that less than 1% of ingested Al is absorbed by the body.[5] In fact, healthy individuals have very low levels of Al because the GI tract, skin, and lungs are effective barriers to Al absorption, and the kidneys efficiently eliminate absorbed Al by excretion.[6]

Recent medical literature has documented toxic effects of Al in patients with impaired renal function, newborns and premature infants, the elderly, patients receiving total parenteral nutrition (TPN), and burn patients. Toxic effects may include encephalopathy, hypercalcemia, vitamin D-refractory osteodystrophy, osteomalacia or aplastic bone disease, proximal myopathy, and microcytic anemia.[7-10] These effects may occur when patients are given Al-containing fluids via parenteral administration, which bypasses the normally protective barriers of the GI tract.

Patients at risk for aluminum toxicity

- Dialysis patients and others with impaired renal function
- Newborns and premature infants
- The elderly
- Patients receiving TPN
- Burn patients

In recent years, the Food and Drug Administration (FDA) has expressed interest in regulating Al content in drugs, blood, foods, and cosmetics. Using a scientific risk-based approach to Al toxicity, the FDA issued regulations for specific language on Al content that must appear in product labeling of TPN drug products, effective July 26, 2004.[11] In addition, the FDA is developing methods for detecting Al in biologic products. Further discussion of this issue can be found on page 9.

Exposure to Aluminum

Aluminum sources—Aluminum is highly prevalent in our environment. Common sources of exposure include water, air, and food. Aluminum cans and containers, foils, baking powder, cake mixes, frozen dough, pancake mixes, self-rising flour, grains, processed cheese, and infant formula are among the food sources that contain Al. OTC products containing Al include deodorants, vaginal douches, baby wipes, skin creams, suntan lotions, toothpaste, buffered aspirin, and some products used to treat hemorrhoids and diarrhea.

Typically, the concentration of Al in water is approximately 70 mcg/L. When multiplying the typical daily Al exposure from water (100 mcg) by the estimated percentage absorbed in humans (0.3%), the daily Al absorbed is 0.005 mcg/kg (Table 1).[5]

Various biologic and pharmaceutical products contain Al, including vaccines, allergy immunotherapy, intravenous (IV) solutions, burn treatments, dialysis solutions, and phosphate-binding gels. Dialysis and TPN solutions are considered elevated sources of exposure. Although the use of tap water to prepare dialysis solutions is an uncommon practice, concentrations of 50 mcg/L of Al in such untreated water would expose the patient to 2400 mcg of Al per day. With an estimated 25% absorption rate, the daily Al absorbed would be 9 mcg/kg (Table 1).[5]

Tables 2 and 3 identify Al levels in common IV and oral solutions. While there was large variation among the lots tested in one study, high Al concentration was found in calcium and phosphate salts, heparin, and normal serum albumin. Also, high Al levels were found in soy and premature-infant formulas.[4]

Safe levels of aluminum—A number of researchers have investigated safe levels of Al in IV solutions. Heyman et al reported that adolescents and adults who received long-term TPN with solutions containing 42 mcg Al/L or less did not experience significant tissue Al loading.[12] A working group formed by the American Society for Clinical Nutrition and the American Society for Parenteral and Enteral Nutrition (ASCN-ASPEN working group) considered this level safe.[13]

Daily intake of Al from TPN solutions was 3.5 mcg/kg in children and 2.2 mcg/kg in adults. This was associated with median serum Al levels of 10.9 mcg/L (range 5.0-26.9), or 7.3 times higher than the control group.[14] One study indicated that there was no decrease in bone formation in preterm infants given Al 3 to 6 mcg/kg/day.[15]

Table 1.
Common Sources of Al for Man, Al Concentration in the Source, Resultant Daily Al Exposure From the Source, Estimated Bioavailability From the Source, and Calculated Amount of Al Absorbed Daily[5]

Source	Al Concentration	Daily Al Exposure	Estimated % Absorbed	Daily Al Absorbed (mcg/kg)[a]
Normal exposure				
Water	Average ~70 mcg/L	100 mcg	0.3	0.005
Food		5000-10,000 mcg	0.1-0.3[b]	0.08-0.5
Air-rural	0.2 mcg/m^3	4 mcg	1.5-2 from lungs[c]	0.001
			0.1-0.3 from GI tract	0.0001
Air-urban	1 mcg/m^3	20 mcg	1.5-2 from lungs[c]	0.006
			0.1-0.3 from GI tract	0.0006
Antiperspirants	5-7.5%[d]	50,000-75,000 mcg	up to 0.012[e]	up to 0.1
Vaccines	150-850 mcg/dose	1.4-8 mcg[f]	100 eventually	0.07-0.4
Elevated exposure				
Antacids/phosphate binders		Up to 5,000,000 mcg	0.1	80
Industrial air	25-2500 mcg/m^3	250-25,000 mcg per work day	1.5-2 from lungs[c]	0.6-8
			0.1-0.3 from GI tract	0.008-1
Allergy immunotherapy	150-850 mcg/dose	7-40 mcg[g]	100 eventually	0.1-0.6
Dialysis solution	If tap water 50 mcg/L	2400 mcg	25	9
TPN solutions	Neonatal/infant 110-270 mcg/L[h]	11-27 mcg/kg	100	11-27
	Adult 40-135 mcg/L[h]	80-270 mcg	100	1.2-4.2

[a] Based on a 65 kg adult except for vaccines (20 kg child) and TPN solution in neonates and infants.
[b] Estimates based on daily urinary Al excretion/daily Al intake from food.
[c] Based on Al exposure in an industrial setting.
[d] Based on 20% Al zirconium glycine complex or 25% Al chlorohydrate in a topical product, which are typical concentrations (POISINDEX information system, Micromedex, Inc, Englewood, CO, USA).
[e] Based on assumption that the percentage of Al absorbed does not change with repeated exposure.
[f] Based on 20 injections in the first 6 years of life and an average weight of 20 kg.
[g] Based on a typical allergen extract treatment schedule and maintenance injections for 3.5 years of one allergen extract.
[h] Based on maintenance fluids and normal neonatal/infant or adult electrolyte supplementation.

Adapted with permission from Yokel RA et al. *Pharmacol Toxicol*. 2001;88:159-167.

Table 2.
Levels of Aluminum in Commonly Administered Intravenous Solutions*[4]

Solution	No. of Lots Tested	Aluminum Content (mcg/liter)
Potassium phosphate (3000 mmol/L)	3	16,598±1801
Sodium phosphate (3000 mmol/L)	1	5977
Calcium gluconate (10%)	5	5056±335
Heparin (1000 units/mL)	3	684±761
Heparin (5000 units/mL)	1	359
Heparin (10,000 units/mL)	1	468
Normal serum albumin (25%)	4	1822±2503
Intralipid	1	195
TPN solution (28% essential amino acid)	6	72±59
5% Dextrose	2	72±1
Sodium chloride (4000 mmol/L)	3	6±4
Potassium chloride (3000 mmol/L)	1	6

* TPN denotes total parenteral nutrition. To convert aluminum values to millimoles per liter, divide by 27. Plus-minus values are means ±SD.

Reprinted with permission from Sedman AB et al. *N Engl J Med*. 1985;312:1337-1343.

Table 3.
Levels of Aluminum in Commonly Used Oral Solutions*[4]

Solution	No. of Lots Tested	Aluminum Content (mcg/liter)
Glucose water	1	20
Tap water (Colorado)	1	12†
Well water (Colorado)	1	5
Breast milk	12	9.9±6.87
Cow's milk-based formula (20 kcal/30 mL)	4	266±192
Cow's milk-based formula, "premature" (24 kcal/30 mL)	4	699±321
Soy formula (20 kcal/30 mL)	4	1478±103
Multivitamins (liquid)	1	32
Nystatin	1	72

* To convert aluminum values to millimoles per liter, divide by 27. Plus-minus values are means ±SD.
† Al content varies depending on locations.

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High levels of Al in IV solutions may be unsafe. Positive bone Al staining was identified in 2 infants from a study group of 10 who received an Al average of 13.4 mcg/kg/day.[16] Infants receiving TPN solutions containing Al 15 to 30 mcg/kg/day demonstrated tissue Al loading. Aluminum toxicity was possible, but not proven.[17] The ASCN-ASPEN working group considered this level unsafe. The group derived its safety standard from the amount of Al administered parenterally that results in tissue loading without clear evidence of tissue dysfunction.[13]

The ASCN-ASPEN working group considered TPN therapy containing Al 60 mcg/kg/day toxic.[13] Adult TPN patients who received solutions containing this level of Al had evidence of tissue Al loading and adverse effects on bone.[17] An earlier study by Klein et al showed that adult patients developed bone disease after receiving Al-contaminated TPN solution daily for 6 to 72 months.[18]

Intravenous therapy with Al-containing solutions—In healthy individuals, the GI tract and lungs act as barriers to greatly limit absorption of Al in the body. Most Al that is absorbed is excreted in the urine, so it is expected that individuals with normal kidney function are not at risk of Al loading from everyday Al exposure.[19]

However, Al levels may become toxic when adults or infants receive IV therapy. In a study of preterm infants by Bishop et al,[20] the results indicate IV feeding with Al-containing solutions is associated with impaired neurologic development. There are 3 reasons for this neurotoxic effect[20]:

- IV therapy enables the Al to bypass the protective actions of the GI tract and the lungs
- Renal function of preterm infants is often impaired, and Al cannot be effectively excreted
- Since Al exposure is high in IV-feeding solutions, the risk of toxicity is also high

Similarly, adults receiving parenteral therapy may experience toxic effects of Al. Again, with parenteral administration, protective mechanisms of the body are bypassed, renal function may be impaired, and Al intake may be high.[19]

In the Klein study, adults who received parenteral nutrition (PN) therapy containing Al developed bone abnormalities. It was determined that the protein source of the PN solution, casein hydrolysate, was the source of the Al contamination.[19] In a study by Ott et al, high Al concentrations of 2313 mcg/L were detected in 10% casein hydrolysate in TPN solutions.[21] When casein hydrolysate was substituted with synthetic amino acids, thereby reducing Al content of the TPN solution, bone conditions improved.[19] Although use of calcium chloride for preparation of TPN solutions at one hospital between 1998 and 1999 showed a significant reduction (up to 92%) in Al levels in newborns, TPN solutions still were not completely free from Al contamination.[22]

Human Serum Albumin

Another IV solution, albumin (human), contains trace amounts of Al.[7,8] Albumin is used for hypovolemic shock, burns, adult respiratory distress syndrome, cardiopulmonary bypass, and neonatal hemolytic disease. Because patients with these conditions receive albumin intravenously and may have renal insufficiency, it is important to consider possible Al toxicity.[7,8]

Aluminum contamination in albumin may be related to collecting, processing, and/or storing the solution.[3,8] The starting material for albumin may already contain Al, and citrate, used in albumin processing, may impact the Al content. Some manufacturers have introduced an extra filtration step to reduce Al and citrate levels. However, over time, any remaining citrate will leach Al from glass storage containers, increasing the Al content of the albumin.

The quality of the glass used to store albumin affects the amount of Al that leaches into the solution. Inoue et al reported that soft glass containers (Type II) reduce the leaching of Al into albumin during storage.[3] The study compared 2 types of glass—hard glass (Type I) and de-alkalized soft glass (Type II). Both types are commonly used as containers for injectable preparations. Acidic, neutral, or alkaline solutions are often stored in hard-glass containers, because this glass type offers higher resistance to chemicals.[3] The hard-glass containers (Type I USP) had an Al oxide content of 5.8%.[3] The soft-glass containers were de-alkalized with sulphurous acid gas and had an Al oxide content of 1.9%. Each container was filled with 50 mL of 25% albumin solution, and the samples were stored at 40°C. Aluminum concentration increased in the sample stored in hard-glass containers, while the Al level of the solution remained the same in the de-alkalized soft-glass containers. Researchers reported that when storing 25% albumin in the Type II glass containers at room temperature, significantly low levels (≤100 ppb) of Al concentration were maintained for at least 2 years.[3]

Effects of Aluminum Toxicity

Low levels of Al in the brain are considered normal. The concentration of Al in the normal mammalian brain is 1 to 2 mcg/g. However, even a small increase in concentration appears to cause toxic effects in sensitive animal species such as cats and rabbits. Studies have shown that 4 mcg/g produced a pathologic response in these sensitive species. Initially, the response pattern shows subtle behavioral changes in learning, memory deficits, and poor motor function, progressing to tremors, incoordination, weakness, and ataxia. Finally, the animal experiences focal seizures and death.

Effects of Al toxicity in humans

Associated

- Dementia
- Encephalopathy
- Learning deficits

Possibly associated

- ALS
- Parkinson's disease
- Alzheimer's disease

In humans, Al toxicity is associated with dementia, encephalopathy, and learning deficits. Degenerative changes occur in the cortex, and toxic effects may be associated with amyotrophic lateral sclerosis (ALS) and Parkinson's disease. These neurologic disorders have been associated with Al toxicity found in patients on the islands of Guam. Aluminum toxicity may be related to Alzheimer's disease and has long been considered a cause of dialysis dementia.[1]

Yokel et al reported Al absorbed in humans or animals appears to persist for a long time. In one human the estimated half-life was 7 years.[5]

Aluminum Toxicity Risk: Patient Profiles

Aluminum contamination of IV solutions presents a high risk of morbidity and mortality to patients with impaired renal function such as dialysis patients.[1,2] Other susceptible patient populations include infants and premature infants, elderly patients, and burn patients. These patients often undergo procedures requiring IV administration of solutions containing Al, which place them at risk of high exposure to Al and its toxic effects. Ingesting Al-containing phosphate-binding gels or infant formulas also may increase the patient's risk of Al toxicity.[1,4] In addition, burn patients are exposed to Al through cutaneous, enteral, and parenteral routes of administration.[23]

Following are 6 patient profiles highlighting individuals at risk for Al toxicity.

Patients with renal dysfunction

The GI tract provides a protective barrier to absorption from oral intake of Al; any metal that is absorbed is excreted from the body primarily through the kidneys. Patients with renal dysfunction have an increased risk of accumulating Al. Parenteral administration also places these patients at risk because the protective effects of the GI tract are bypassed. This population requires special attention in order to reduce the intake of Al.[1]

Toxic levels of Al may occur during prolonged parenteral administration of medications contaminated with Al. This is an especially high-risk situation for patients with impaired kidney function. Patients (including premature neonates) receiving parenteral administration of Al at levels greater than 4 to 5 mcg/kg/day may be at risk of high levels of Al accumulation, which have been associated with central nervous system toxicity and bone toxicity. At lower levels of administration, tissue loading may occur.[24]

Ingestion of Al-containing phosphate-binding gels also places patients at risk of Al toxicity. Patients with chronic renal failure are often treated with binding gels to counteract the effects of hyperphosphatemia. Because these patients are unable to excrete phosphate normally, these binding gels help reduce hyperphosphatemia. However, the use of phosphate binders appears to cause Al toxicity in patients with chronic renal failure. This results from the patient's reduced excretion combined with an increase in Al intake from the binding gels.[1,25] The American Academy of Pediatrics discourages the use of Al-containing phosphate-binding gels in infants and children with renal failure.[25,26]

Dialysis patients

In the past, Al was a known contaminant of water used to prepare dialysate for hemodialysis patients with end-stage renal disease.[27] Aluminum accumulation in tissue causes dialysis encephalopathy, also known as dialysis dementia. Increased tissue concentration appears to be responsible for one type of osteomalacia. Both encephalopathy and osteomalacia are associated with long-term, intermittent hemodialysis.[10] Once acceptable standards for Al concentration in dialysate were recognized, and dialysis units worldwide effectively monitored Al in water, the incidence of dementia was reduced significantly.[28] To maintain strict standards required for water used in dialysate preparation, most dialysis centers use methods of water purification that may include a combination of water softener, activated carbon filters, deionizers, and reverse osmosis.[29]

Berend et al[29] reported an epidemic of acute Al encephalopathy that occurred in a dialysis unit on the island of Curacao. The dialysis center prepared dialysate with water obtained from a new water distribution pipe lined with cement mortar. Unknown to physicians on the dialysis unit at the time, 27 patients were exposed to dialysate made from water that was contaminated with Al that had leached from the cement mortar. Ten patients died from acute Al encephalopathy, and 17 patients survived, experiencing little or no symptoms at all. Based on this tragic experience, the researchers urge the medical community to monitor water used to prepare dialysate before and after water treatment. In addition, they recommend that dialysis centers use purification processes including reverse osmosis to assure water safety.[29]

Infants

Infant formulas, especially soy-based formulas, contain Al. Aluminum content in infant formulas is higher than in human breast milk or in cow's milk. Specialized formulas for premature infants contain even higher Al content than standard formulas.[4] For adults, typical dietary intake of Al is 40 to 50 mcg/kg of body weight/day. In comparison, infants on soy formula may consume as much as 250 mcg/kg/day of Al. Further studies are needed to determine the risks and effects of consuming large amounts of soy formula.[4]

While the GI tract would naturally protect the infant's body from Al accumulation, one theory suggests that Al absorption could be increased due to increased permeability of the infant's intestine. In healthy infants, it is believed that most of the Al ingested is excreted, and Al absorption does not occur.[2] Most likely, preterm infants with impaired renal function are at highest risk of Al toxicity, because less of the absorbed Al would be excreted.[2] Because premature infant formulas provide significant nutritional benefits, the American Academy of Pediatrics continues to recommend their use, but it suggests further investigation into the possible risk of Al accumulation in premature infants.[26]

Premature infants receiving IV therapy

Intravenous therapy contaminated with Al causes Al loading, which places premature infants at high risk of Al intoxication. Fracturing osteomalacia, encephalopathy, and microcytic anemia are the classic manifestations of Al toxicity. However, Sedman et al[4] explain that these abnormalities are not easily defined in premature infants. For example, the histologic data used to diagnose osteomalacia do not exist for neonates, and anemia and encephalopathy in premature infants may occur for reasons other than Al toxicity. Because Al is associated with bone and neurologic toxicities, researchers suggest that small children with rapidly maturing skeletal and nervous systems may be unduly susceptible to such toxicity.[4]

The Sedman study reports high concentrations of Al in bone, urine, and plasma of infants undergoing IV therapy. Parenteral exposure to Al and impaired renal function may place premature infants at higher risk of Al accumulation.[4]

More recently, Bishop et al[20] reported on the potential neurotoxicity of IV feeding solutions contaminated with Al in a prospective randomized study that evaluated 227 premature infants with gestational ages under 34 weeks. Infants were randomized to receive standard IV feeding solutions (total Al intake: 45 mcg/kg/day) or Al-depleted solutions (total Al intake: 4-5 mcg/kg/day). The Mental Scale of the Bayley Scales of Infant Development was used to evaluate the neurologic development of the 182 surviving infants at 18 months of age. Infants receiving the standard IV feeding solution had a lower mean Bayley Mental Development Index than infants receiving the Al-depleted solutions. The authors conclude that Al is potentially neurotoxic, and long-term IV feeding is associated with impaired neurologic development in premature infants.[20]

Ott et al reported that patients with normal renal function receiving long-term TPN demonstrated evidence of Al loading.[21] With PN, patients receive 100% of the Al load because PN bypasses the GI tract.[2] The FDA recommends that the concentration of Al in parenteral solutions should be limited to 25 mcg/L.[24]

Elderly patients

It has been suggested that there is a possible Al connection with dementia and Alzheimer's disease.[1] In 1980, Perl and Brody suggested that Al might be related to Alzheimer's disease, adding that the finding could not be explained.[30] In later studies, Perl and colleagues suggested that Al might play an active role in dementia and ALS found among patients on the islands of Guam.[31] Some studies have shown that Al levels are higher in individuals with probable Alzheimer's disease compared to those of patients with other types of dementia and compared to healthy individuals of similar ages. Generally, researchers agree that the association of Al and Alzheimer's disease and other neurologic disorders requires further explanation.[2,10]

It appears that the elderly may be vulnerable to Al toxicity. In the report by Berend et al, of 27 patients who were treated accidentally with Al-containing dialysate, 10 patients died from acute neurotoxicity. The researchers noted that the nonsurvivors were older, had lower body weight, and had lower serum albumin concentrations, and many in the older population had diabetes, suggesting that general health may affect Al susceptibility and survival.[29]

A study of acute Al neurotoxicity at a dialysis center suggested older, more debilitated patients—those with lower body weight, lower serum albumin concentrations, and diabetes—may be more vulnerable.

Burn patients

Unless they are treated with low-Al albumin, burn patients may be at risk of high Al intake because they receive large quantities of albumin and often have impaired renal function. These factors combined place burn patients at higher risk of Al loading. Since excretion is the body's mechanism for eliminating Al, renal impairment may contribute to high serum Al concentrations and accumulation.[18,27]

Accumulation of Al may play a role in the development of bone lesions in severely burned patients. The Klein et al study assessed the risk of Al loading from cutaneous, enteral, and parenteral exposure. Baths used in treating burn patients cutaneously expose patients to as much as 8 mg of Al per bath. Normally, the skin provides a barrier to Al exposure; because burn patients' skin is damaged, the risk of Al intake is unknown. Enteral intake of Al is similar to that of normal dietary intake of 2 to 5 mg daily.[23]

The greatest risk appears to be parenteral administration of IV solutions containing Al. Albumin and calcium gluconate are implicated as the cause of Al loading, because IV administration of these solutions bypasses the protective effects of the GI tract. The authors note that substitution with an alternate brand of albumin and calcium chloride could decrease parenteral Al by up to 95%. This reduction in Al load could potentially protect burn patients from the effects of Al toxicity.[23]

Regulatory Considerations

The FDA has a strong interest in Al toxicity in all products, including medications, blood, foods, cosmetics, and industrial exposure. Currently, the FDA's Center for Biologics Evaluation and Research (CBER) is developing methods for detecting Al in biologic products.

In January 2000, the FDA issued regulations for the labeling of Al content in products used for TPN. Over the course of several years, there were slight revisions to the information provided. In the final ruling, the FDA notes that these requirements are being added because of evidence linking the use of TPN containing Al to increased morbidity and mortality of patients receiving this therapy, particularly premature infants and patients with impaired renal function.[24]

The FDA's regulations of TPN involve labeling requirements for Al content in large volume parenterals (LVPs), small volume parenterals (SVPs), and pharmacy bulk packages (PBPs). The effective date of these requirements is July 26, 2004.[11]

Effective July 26, 2004, FDA regulations for TPN labeling require listing Al content

- Large volume parenterals
- Small volume parenterals
- Pharmacy bulk packages

The new requirements limit Al content for all LVPs to 25 mcg/L, which the FDA notes is both feasible and necessary for the safe and effective use of LVPs used in TPN therapy. Other highlights of the final ruling specify that the maximum level of Al at expiry must be stated on the *immediate* container label, so that if the maximum level of Al is 25 mcg/L or less, the label should read: *Contains no more than 25 mcg/L of Al.*[24] Another labeling requirement involves lyophilized powder used to prepare TPN solutions. Again, the maximum level at expiry must be printed and the label should state: *When reconstituted in accordance with the package insert instructions, the concentration of Al will be no more than 25 mcg/L.*[24]

Concerns that glass leaching could cause Al content to increase to unacceptable levels by the time the product expires can be addressed through the use of non-glass containers, according to the FDA.[24]

New TPN Warning Language

The new FDA requirements for package inserts used in TPN products (LVPs, SVPs, and PBPs) require a warning statement to be included in the "Warnings" section of the labeling. The warning must contain the following language[24]:

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

Albumin Labeling

In the United States, Al toxicity and levels of Al in albumin are of increasing concern because accumulation of Al in patients with chronic renal insufficiencies has led to toxic manifestations such as hypercalcemia, vitamin D-refractory osteodystrophy, anemia, and severe progressive encephalopathy.

In Canada, a new warning requirement for albumin products has been added: *Use of albumin preparations should be carefully evaluated for risk and benefit in pediatric treatment and should not be used to treat infants and patients on hemodialysis if it contains greater than 200 mcg/L of aluminum.* In addition, some European countries, China, and many other countries now require Al content of albumin to be less than 200 mcg/L. Talecris Biotherapeutics offers a low-Al albumin product that is not more than 200 mcg/L through the indicated shelf life in Type II glassware.

Other products with concerns involving Al toxicity include antacids, dietary supplements, color additives, tanning agents, and deodorants.

Recommendations

Once safe standards were established for Al concentration in water used to prepare dialysis solutions, Al toxicities, including dialysis encephalopathy and fracturing osteomalacia, were reduced dramatically.[4,26] The reduced incidence of clinical manifestations related to Al toxicity highlights the importance of reducing Al content in all medical products.

Although standards for safe levels of Al in dialysates are useful, the experience of Berend et al[29] suggests that monitoring water before and after it is treated is prudent. Because Al levels in water depend on geographic location,[2] water purification for hemodialysis is essential.[29] Reverse-osmosis water treatment is recommended to reduce Al contamination of dialysate water.[28,32]

Recommended safety measures to prevent Al toxicity

- Monitoring and purification of dialysate water
- Reduction of Al content in infant formulas
- Reduction of Al content in IV solutions
- Selection of lowest-possible Al content therapies for high-risk patients

Aluminum content in all infant formulas should be reduced. It is especially important to reduce the Al content of soy formulas and specialized formulas made for premature infants, because these have a higher Al content than standard infant formulas. For infants with renal failure and for premature infants, it is important to monitor Al contamination of water used in preparation of formulas for these infants.[26]

To minimize the toxic effects of Al, IV solutions should be continuously monitored to reduce Al contamination.

Special attention from healthcare professionals is vital for patients at risk of Al toxicity. This unique and varied population at risk includes patients with impaired renal function, infants and premature infants, elderly patients, patients receiving TPN, and burn patients. Care is needed to assure that these patients receive medications with the lowest possible Al content. It is also important to minimize the use of therapies that involve long-term, large-volume administration of IV solutions contaminated with Al.

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Talecris BIOTHERAPEUTICS

Talecris Albumin Products
Building on a legacy of excellence

Plasbumin®–5
Albumin (Human) 5%, USP

Who needs low aluminum albumin?

Many of your patients may be at high risk for aluminum toxicity from parenteral treatments.[1] These individuals include newborns and premature infants, the elderly, patients with impaired renal function, patients receiving total parenteral nutrition, and burn patients.[1-4] Now there's one albumin for all your patients.

Low aluminum albumin from Talecris.

Albumin is contraindicated for certain patients who are at special risk of developing circulatory overload, eg, those with a history of congestive cardiac failure, renal insufficiency, or stabilized chronic anemia. Albumin is also contraindicated in patients with a history of allergic reaction to albumin. Albumin human products are made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease.

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Ordering information for Plasbumin®–5:
NDC 13533-690-20 50 mL
NDC 13533-690-25 250 mL

For clinical or technical information regarding Plasbumin®, please contact Talecris Clinical Communications at 1-800-520-2807.

www.Plasbumin.com

Please see complete prescribing information on adjacent page.

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Talecris BIOTHERAPEUTICS

Talecris Albumin Products
Building on a legacy of excellence

Albumin (Human) 5%, USP
Plasbumin®-5

DESCRIPTION

Albumin (Human) 5%, USP (Plasbumin®-5) is made from pooled human venous plasma using the Cohn cold ethanol fractionation process. Part of the fractionation may be performed by another licensed manufacturer. It is prepared in accordance with the applicable requirements established by the U.S. Food and Drug Administration.

Plasbumin-5 is a 5% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The aluminum content of the product is not more than 200 µg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-5 must be administered intravenously.

Each vial of Plasbumin-5 is heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses.

CLINICAL PHARMACOLOGY

Plasbumin-5 is oncotically equivalent volume for volume to normal human plasma.

When administered intravenously to an adequately hydrated subject, the oncotic (colloid osmotic) effect of Plasbumin-5 is to expand the circulating blood volume by an amount approximately equal to the volume infused. It is primarily used in the treatment of shock associated with hemorrhage, surgery, trauma, burns, bacteremia, renal failure, and cardiovascular collapse.[1]

Albumin is a transport protein and it may be useful in severe jaundice in hemolytic disease of the newborn.[2] This could also be of importance in acute liver failure where albumin might serve the dual role of supporting plasma oncotic pressure, as well as binding excessive plasma bilirubin.[1]

INDICATIONS AND USAGE

Emergency Treatment of Hypovolemic Shock

Plasbumin-5 is iso-oncotic with normal plasma and on intravenous infusion will expand the circulating blood volume by an amount approximately equal to the volume infused. In conditions associated mainly with a volume deficit, albumin is best administered as a solution (Plasbumin-5); but where there is an oncotic deficit, Albumin (Human) 25%, USP (Plasbumin®-25) may be preferred. This is also an important consideration where the treatment of the shock state has been delayed. If Plasbumin-25 is used, appropriate additional crystalloid should be administered.[1]

Crystalloid solutions in volumes several times greater than that of Plasbumin-5 are effective in treating shock in younger individuals who have no preexisting illness at the time the incident. Older patients, especially those with preexisting debilitating conditions, or those in whom the shock is caused by a medical disorder, or where the state of shock has existed for some time before active therapy could be instituted, may not tolerate hypoalbuminemia as well.[1]

Removal of ascitic fluid from a patient with cirrhosis because changes cardiovascular function and even result in hypovolemic shock. In such circumstances, the use of albumin infusion may be required to support the blood volume.[1]

Burn Therapy

An optimal therapeutic regimen with respect to the administration of colloids, crystalloids, and water following extensive burns has not been established. During the first 24 hours sustaining thermal injury, large volumes of crystalloids are usually used to restore the depleted extracellular fluid volume. Beyond 24 hours albumin can be used to maintain plasma colloid osmotic pressure. Plasbumin-25 may be preferred for this purpose.[1]

Cardiopulmonary Bypass[1]

With the relatively small priming volume required for modern pumps, preoperative dilution of the blood using albumin and crystalloid has been shown to be safe and well-tolerated. Although the limit to which the hematocrit and plasma protein concentration can be safely lowered has not been defined, it is common practice to adjust the albumin/crystalloid pump prime to achieve a hematocrit of 20% and a plasma albumin concentration of 2.5 g per 100 mL in the patient.

Acute Liver Failure[1]

In the uncommon situation of rapid loss of liver function, with or without coma, administration of albumin may serve the double purpose of supporting the colloid osmotic pressure of the plasma as well as binding excess plasma bilirubin.

Sequestration of Protein Rich Fluids[2]

This occurs in such conditions as acute peritonitis, pancreatitis, mediastinitis, and extensive cellulitis. The magnitude of loss into the third space may require treatment of reduced volume or oncotic activity with an infusion of albumin.

Situations in Which Albumin Administration is Not Warranted[1]

In chronic nephrosis, infused albumin is promptly excreted by the kidneys with no relief of the chronic edema or effect on the underlying renal lesion. It is of occasional use in the rapid "priming" diuresis of nephrosis. Similarly, in hypoproteinemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency, and undernutrition, the infusion of albumin as a source of protein nutrition is not justified.

CONTRAINDICATIONS

Certain patients, e.g., those with a history of congestive cardiac failure, renal insufficiency or stabilized chronic anemia, are at special risk of developing circulatory overload. A history of allergic reaction to albumin is a specific contraindication for usage.

WARNINGS

Plasbumin-5 is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Solutions which have been frozen should not be used. Do not use if turbid. Do not begin administration more than 4 hours after the container has been entered. Partially used vials must be discarded. Vials which are cracked or which have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms. Plasbumin-5 contains no preservative.

PRECAUTIONS

General

Patients should always be monitored carefully in order to guard against the possibility of circulatory overload. Albumin (Human) 5%, USP (Plasbumin®-5) is iso-oncotic with normal plasma and will not tend to aggravate tissue dehydration. Appropriate additional crystalloids should be administered, if required by the patient, to maintain normal fluid balance.

In hemorrhage, the administration of albumin should be supplemented by the transfusion of whole blood to treat the relative anemia associated with hemodilution.[3] When circulating blood volume has been reduced, hemodilution following the administration of albumin persists for many hours. In patients with a normal blood volume, hemodilution lasts for a much shorter period.[4-6] The rapid rise in blood pressure, which may follow the administration of a colloid with positive oncotic activity, necessitates careful observation to detect and treat severed blood vessels which may not have bled at the lower blood pressure.

Drug Interactions

Plasbumin-5 is compatible with whole blood and packed red cells, as well as the standard carbohydrate and electrolyte solutions intended for intravenous use. It should not be mixed with protein hydrolysates, amino acid solutions nor those containing alcohol.

Pregnancy Category C

Animal reproduction studies have not been conducted with Plasbumin-5. It is also not known whether Plasbumin-5 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Plasbumin-5 should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Adverse reactions to albumin are rare. Such reactions may be allergic in nature or be due to high plasma protein levels from excessive albumin administration. Allergic manifestations include urticaria, chills, fever, and changes in respiration, pulse and blood pressure.

DOSAGE AND ADMINISTRATION

Plasbumin-5 should always be administered by intravenous infusion. The choice between the use of Plasbumin-5 and Albumin (Human) 25%, USP (Plasbumin®-25) depends upon whether the patient requires primarily volume (Plasbumin-5) or primarily colloid osmotic activity (Plasbumin-25). Below an oncotic level of 20 mm Hg (equal to a total serum protein concentration of 5.2 g per 100 mL) there is evidence which suggests that the risk of complications increases.[1] When the oncotic pressure drops below this level, the patient should be treated with Plasbumin-25 together with diuretics. This is especially important in high risk patients who have undergone abdominal, cardiovascular, thoracic or urologic surgery or who have acute bacteremia.

The volume administered and the speed of administration should be adapted to the response of the individual patient.

A number of factors beyond our control could reduce the efficacy of this product or even result in harmful effects following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

Hypovolemic Shock

The volume infused should be related to the estimated volume deficit and the speed of administration adapted to the response of the patient.

In neonates or infants, Plasbumin-5 may be given in large amounts.[7] The recommended dose is 10 to 20 mL/kg equivalent to 0.5 to 1.0 g albumin/kg body weight.

Burns

After a burn injury (usually beyond 24 hours) there is a close correlation between the amount of albumin infused and the resultant increase in plasma colloid osmotic pressure. The aim should be to maintain the plasma albumin concentration in the region of 2.5 ± 0.5 g per 100 mL with a plasma oncotic pressure of 20 mm Hg (equivalent to a total plasma protein concentration of 5.2 g per 100 mL).[1] This is best achieved by the intravenous administration of Plasbumin, usually as Plasbumin-25. The duration of therapy is decided by the loss of protein from burned areas and in the urine. In addition, oral or parenteral feeding with amino acids should be initiated, as the long-term administration of albumin should not be considered as a source of nutrition.

Other dosage recommendations are given under the specific indications referred to above.

Preparation for Administration

Remove seal to expose stopper. Always swab stopper top immediately with suitable antiseptic prior to entering vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Only 16 gauge needles or dispensing pins should be used with 20 mL vial sizes and larger. Needles or dispensing pins should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

HOW SUPPLIED

Plasbumin-5 is available in 50 mL, 250 mL and 500 mL rubber-stoppered vials. Each single dose vial contains albumin in the following approximate amounts:

NDC Number	Size	Grams Albumin
13533-690-20	50 mL	2.5
13533-690-25	250 mL	12.5
13533-690-27	500 mL	25.0

STORAGE

Store at room temperature not exceeding 30°C (86°F). Do not freeze. Do not use after expiration date.

CAUTION

Rx only

U.S. federal law prohibits dispensing without prescription.

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