Invited Commentary

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Aluminum Contamination of Parenteral Nutrition Fluids

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It has been >25 years since the clinical manifestations of aluminum ingestion from parenteral fluids were reported.[1,2] Impaired bone growth, especially in adults, and delays in mental development in neonates are the predominant effects observed. Aluminum is ubiquitous, which unfortunately leads to its undesired presence in parenteral products. Of these parenteral products, parenteral nutrition (PN) is a substantial source of aluminum.[3] Normally, aluminum is easily eliminated in the urine. Adult patients with renal compromise and neonates are the patient populations at greatest risk of developing toxicity from the aluminum present in parenteral fluids. As a result, the U.S. Food and Drug Administration (FDA) published a rule[4] requiring manufacturers of products used in the preparation of PN fluids to label the content of aluminum in their products. For large-volume parenterals, there should not be >25 µg/L aluminum; for small-volume parenterals, the potential maximum amount at expiry of the product should be on the label. The label should include a warning that patients with impaired renal function, including premature neonates, who receive >4–5 µg/kg/d of aluminum may experience central nervous system and bone toxicity. Because this regulation applies to industry only, there was confusion among clinicians as to what their role should be.[5] A.S.P.E.N. issued a statement on aluminum in PN solutions[6] that provides some guidance to clinicians:

- Those ordering and preparing PN should be aware of the potential for aluminum contaminants in these products.
- The compounding pharmacy may wish to develop a database of the aluminum content of products used in preparation of PN.
- Clinicians may want to purchase equivalent products that have the lowest aluminum content and monitor changes in the pharmaceutical market that affects aluminum concentrations.
- All healthcare providers involved with PN should attempt to limit aluminum exposure in at risk patients.
- Patient monitoring of aluminum toxicity may not be possible or reliable in many clinical settings.

Since the FDA rule, we have learned more about aluminum in PN fluids as well as other sources of aluminum in patients receiving parenteral therapy. In PN, calcium and phosphate salts as well as cysteine hydrochloride are major contributors to the overall aluminum content in adult and neonatal formulations.[3,7] Using the labeled amount of aluminum in PN products to estimate aluminum content, Driscoll and Driscoll[8] found that it is virtually impossible to prepare a PN that is less than the FDA limit of 5 µg/kg/d and meet the nutritional needs of the patient. Speerhas and Seidner[9] found that the measured content of aluminum was 7–10 times lower than that estimated from the product labels. However, the amount of aluminum in all of the neonatal and pediatric solutions tested exceeded the FDA limits whereas only 2 of the adult formulations exceeded the limit. Canada[10] reviewed the studies of aluminum contamination in PN fluids and found that those prepared in other countries had less aluminum than those prepared in the United States. The lower aluminum content was attributed to the use of an organic phosphorus source that contains less aluminum than the inorganic salts used in the United States. The organic phosphorus is also more compatible with calcium chloride, which has lower aluminum content than the gluconate salt. Canada also reported on the success in Germany by Frey and Maier[11] in reducing aluminum concentration by 96% as the result of repackaging calcium gluconate from glass containers to polyethylene vials. This reduced the daily intake of pediatric patients receiving PN from a range of 30–40 µg/kg/d down to 2–3 µg/kg/d.

Bohrer et al[7,12,13] and de Oliveira et al[14] provide further credence to the FDA rule and remind us that aluminum continues to be a concern that should be addressed. In previous publications, this group demonstrated that aluminum in commercial products was present in the raw materials of the product but the amount did not fully explain the entire content of aluminum measured.[7] This group also determined that the amount of aluminum

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leached from glass containers with rubber closures is a significant contributor to aluminum present in parenteral products.[12,13] In their article published in this issue of *JPEN*, de Oliveira et al[14] demonstrate that product manipulation during preparation and the products used for parenteral administration contribute significantly to the amount of aluminum infused to neonates. All steps involved in the preparation and administration of intravenous solutions for premature infants were assessed for potential contribution to the daily aluminum load being administered. Commercial products used in PN preparation, injectable medications, and products used in packaging and administering parenteral products (bags, burettes, syringes, and administration sets) were contaminated with aluminum. Although commercial products were the main source of aluminum, product manipulation, containers, and administration sets increased aluminum levels by 40%. This is a substantial amount of aluminum not originally considered in the FDA rule.

Neonates are the patient population most likely to be adversely affected by aluminum loads infused in parenteral therapy. In the United States, calcium and phosphorus intakes need to be eliminated or substantially decreased below nutritional needs for neonates in order to limit the aluminum load presented by PN. An alternative to reducing aluminum loads to neonates is to not administer PN because the aluminum content of PN prepared in the United States is too high. These are not acceptable options to clinicians caring for neonates.

Aluminum is present in all products used in parenteral therapy. Even though PN contributes the majority of aluminum that is infused, drug products, administration sets, and product manipulation will also influence the final amount of aluminum infused on a daily basis. The new information provided by de Oliveira et al[14] reinforces the recommendation that clinicians have a heightened awareness of aluminum contamination of parenteral products ordered and administered in their daily practice. Ingredients with the lowest amount of aluminum should be used in the preparation of PN. The use of products packaged in glass containers with rubber closures should be avoided. We as clinicians should insist that small-volume parenterals be packaged in polyethylene containers. Finally, it may be time to partner with manufacturers to bring to the U.S. market organic phosphorus products for PN compounding like those that have allowed our European colleagues to substantially limit the amount of aluminum contamination in their PN fluids.

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