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Robert A. Yokel
University of Kentucky, ryokel@email.uky.edu

Wesley R. Harris
ALKYMOS Inc.

Christopher D. Spilling
ALKYMOS Inc.

Vasilij P. Abramov
CreoSalus

See next page for additional authors

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Authors

Robert A. Yokel, Wesley R. Harris, Christopher D. Spilling, Vasiliy P. Abramov, Jason M. Lone, and Robert J. Kuhn

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CLINICAL INVESTIGATION

A Filtration System That Greatly Reduces Aluminum in Calcium Gluconate Injection, USP Used to Prepare Parenteral Nutrition Solutions

Robert A. Yokel, PhD,^{1,2} Wesley R. Harris, PhD,^{2,3} Christopher D. Spilling, PhD,^{2,3} Vasily P. Abramov, MS,⁴ Jason M. Lone, MEng,⁴ and Robert J. Kuhn, PharmD^{2,5}

¹Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky,

²ALKYMOS Inc, Lexington, Kentucky, ³Department of Chemistry and Biochemistry, University of Missouri, St Louis, Missouri, ⁴CreoSalus, Louisville, Kentucky, ⁵Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, Kentucky

OBJECTIVE: The study objective was to reduce aluminum (Al) in Calcium Gluconate Injection, US Pharmacopeia (USP) used in the preparation of parenteral nutrition (PN) solutions.

METHODS: A flow-through filter containing an immobilized chelator that complexes Al from Calcium Gluconate Injection, USP as it flows through the filter was designed, refined by design modifications, and extensively tested. When a small-volume parenteral vial containing 100 mL of Calcium Gluconate Injection, USP is connected on the inlet side of the filter, and the outlet side is connected to an evacuated receiving vial, the filtered solution is drawn into the receiving vial. This constitutes a complete system to remove Al from Calcium Gluconate Injection, USP.

RESULTS: The extent of Al removal is flow rate dependent. At a flow rate of 1 mL/min approximately 85% of the Al was removed from calcium gluconate solution. PN solutions have been reported to deliver 15 to 23 mcg/kg/day Al to neonates. Given that Calcium Gluconate Injection, USP provides 85% of the Al in neonatal PN solutions, removal of 85% of the Al from this source was calculated to reduce Al delivered to most neonates to <5 mcg/kg/day.

CONCLUSIONS: A point-of-use, self-contained, single-use, disposable, Al-complexing filter has been created. It was calculated to reduce Al delivered in PN solutions by 72%, resulting in daily Al delivery below the level that results in Al accumulation associated with central nervous system and bone toxicity to all but the smallest (<1 kg) infants.

INDEX TERMS: aluminum, calcium gluconate, parenteral nutrition

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INTRODUCTION

Aluminum (Al) is a contaminant of small- and large-volume parenteral (SVP and LVP) solutions used to compound parenteral nutrition (PN) solutions. It produces no beneficial effects in the human but has the potential to produce toxicity to the brain, skeletal system, liver, and erythropoietic system. Premature neonates are the population at greatest risk for Al toxicity because of their immature renal function (the primary route of Al elimination). A standard PN solution that delivered 45 mcg/kg/day Al was given to premature neonates for about 10

days and resulted in significant reduction in the Bayley Mental Development Index score at age 18 months compared with infants who received approximately 15% as much Al.¹ A follow-up study a decade later showed the children who received the PN solution that delivered 45 mcg/kg/day Al had less lumbar spine bone mineral content than those who received 15% as much Al.² Al may contribute to the vitamin D-resistant rickets seen in neonates given PN.^{3,4} Al in PN solution may also contribute to cholestasis.^{5,6} A microcytic, hypochromic anemia that appears in adult dialysis patients⁷ correlates with plasma Al concentration.⁸ This has been associated with

elevated Al in pediatric patients,⁹ but the association of anemia and Al exposure has evidently not been investigated in neonates.

The amount of Al given to neonates in PN solutions was estimated^{10,11} based on the maximum Al content stated on the product label, which ranged up to 12,500 mcg/L. Such calculations do not document the actual amount of Al delivered to neonates by PN, given that the product's Al concentration may be considerably less than the maximum stated on its label.

Al delivered to 10 neonatal patients weighing 1.5 to 2.5 kg was determined by quantifying the Al in prepared PN solutions. This showed a mean \pm SD of 15.2 ± 8.0 mcg/kg/day.¹² Based on Al eliminated in the urine, 56% of the intake was retained by these infants. Similarly, the measured Al in PN solutions given to 40 neonates revealed a mean daily delivery ranging from 23 mcg/kg in patients weighing <1 kg to 15 mcg/kg in 4- to 6-kg patients.¹³ This level of Al delivery is well above the 4 to 5 mcg/kg/day Al load that results in Al accumulation associated with central nervous system and bone toxicity noted in the Food and Drug Administration's (FDA's) labeling requirement that addresses Al in SVP and LVP solutions.¹⁴

The Al concentration of PN components and prepared PN solutions is not routinely quantified before their use. As a result, the amount of Al given to patients is not routinely known. The main source of the Al in PN solutions is Calcium Gluconate Injection, US Pharmacopeia (USP), which was shown to contribute 78% to 89% of the Al in PN solutions.¹⁵⁻¹⁸ Al increases over time in calcium gluconate packaged in glass vials because of the Al complexing ability of gluconate, which leaches Al from the glass storage container.^{19,20} The clinical problem of Al contamination in components used to compound PN solutions has been recognized for nearly 30 years. It was recently reviewed²¹⁻²⁴ and presented at an international aluminum conference.²⁵

To reduce the amount of Al delivered to neonates, it was suggested to use component SVP and LVP solutions that have the smallest maximum Al concentration according to the product label, and to minimize the shelf life of calcium gluconate.^{10,23,26} Even with use of these approaches it is currently not possible to bring the Al delivered to neonates by PN to less than 4 to 5 mcg/kg/day.^{21,23} To address this problem

we developed a filter that removes most of the Al from Calcium Gluconate Injection, USP.

MATERIALS AND METHODS

To reduce the amount of Al delivered in PN solutions, we considered the steps in the PN preparation process amenable to Al removal, the preferable method of Al removal, and the application of that method. Selective removal of Al from the compounded PN solution was deemed not possible because there were no known methods to remove Al without also removing essential trace metals, such as iron and copper. The focus was then on Al removal from its primary source, Calcium Gluconate Injection, USP. Removal of Al by complexation to an immobilized chelator (resin), so that the chelator did not enter the calcium gluconate solution, was selected as the most practical approach. Consideration of both Al complexing ability by the chelator and ease of synthesis suggested incorporation of hydroxamic acid, the functional moiety of desferrioxamine (deferoxamine), used clinically to reduce Al accumulation and toxicity.^{27,28}

The ligand exchange rate for Al is rather slow,²⁹ and the rate of calcium gluconate addition to PN solutions as they are being prepared by commercial compounders is very high. Therefore, it was concluded that Al extraction efficiency would probably be very low if the resin were exposed to the Al-contaminated calcium gluconate solution flowing at this high rate. This was confirmed by preliminary studies using a simple flow-through cartridge containing the resin that showed an inverse relationship between flow rate and Al extraction efficiency. This dictated a point of application that was off-line from the preparation of PN solution (not used in-line between the calcium gluconate source and the bag containing the PN being prepared). We investigated several concepts. The use of a recirculating peristaltic/roller or syringe pump to push the calcium gluconate through a cartridge containing the resin had the disadvantages of the required equipment, the requirement to validate electrical/power compliance, the need for the person using the pump to select the proper flow rate, and the need for the pump to automatically stop at the end of filtration. Space constraints in the laminar flow hood were also of major concern with this approach. A "tea bag" approach in which the resin would be con-

tained in a semipermeable membrane (bag) was found to benefit from agitation for good efficiency. However, this would require auxiliary equipment, a bag in a bottle is not standard practice in the hospital's IV/PN preparation room, and there was concern the bag may occlude the outlet when the calcium gluconate solution was withdrawn. We investigated loose resin beads in a vial that would receive the calcium gluconate. The resin beads would have to be retained by a membrane. We considered that the end users might be concerned that the membrane did not retain all of the beads. We found greater Al extraction with the resin in a flow-through cartridge compared with a suspension of the resin in the calcium gluconate.

As an alternative to pushing the calcium gluconate through the resin, we investigated using partial vacuum to pull it through a cartridge containing the resin. This was achieved using a partially evacuated receiving vial to pull the calcium gluconate solution through a cartridge containing the resin, and a flow restrictor to control the fluid flow rate (the ALKYMOS ACE filter, ALKYMOS Inc, Lexington, KY). This approach requires no additional equipment. A flow rate of 1 mL/min was selected as a compromise between the increased Al extraction efficiency achieved with longer extraction time and the resultant duration of the extraction. This flow rate requires 100 minutes to remove Al from 100 mL of calcium gluconate. This approach was tested with commercial Calcium Gluconate Injection, USP, 100-mL vials (from APP Pharmaceuticals LLC, Schaumburg, IL) and Calcium Gluconate Injection, USP to which additional Al was added to approach the maximum Al concentration of some Calcium Gluconate Injection, USP products (12,500 mcg/L). This was accomplished by adding Al (as the nitrate) to give higher initial Al concentrations of 8000 and 11,500 mcg/L and allowing equilibration for >1 week. The Al concentration was quantified using inductively coupled plasma mass spectrometry (Agilent 7500cx, Santa Clara, CA).

The above experiments were conducted with non-gamma-irradiated filters. In addition, 3 filters were exposed to 25-kGy and 3 filters to 50-kGy gamma irradiation, and Al and calcium concentrations before and after filtration of Calcium Gluconate Injection, USP were determined using inductively coupled plasma mass spectrometry. Results were compared to a standard curve created from an Ultra Scientific (N. Kingstown, RI)

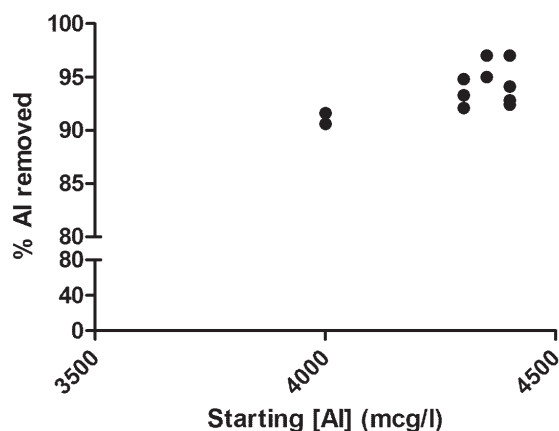


Figure 1. Percentage of aluminum removed from commercial Calcium Gluconate Injection, USP by the ALKYMOS ACE filter. Results are from 4 separate experiments, each conducted with 2 to 4 replicates.

Analytical Solutions multielement standard. A *PlasmaCAL* multielement calibration standard (SCP Science, Champlain, NY) was used to prepare the intercalibration verification standard. Scandium was added as the internal standard to all samples and standards for the Al and calcium analyses.

Using the extent of Al extraction from Calcium Gluconate Injection, USP by the gamma-sterilized ALKYMOS ACE filters, we calculated the reduction in total Al exposure expected in patients receiving PN solutions, assuming that 85% (based on the 78%-89% described in the introduction¹⁵⁻¹⁸) of the Al in PN solutions is derived from Calcium Gluconate Injection, USP. Poole et al¹³ measured the Al delivered to 40 neonates receiving PN. The calculated Al exposure reduction was applied to the results of Poole et al¹³ to predict the Al load that would be delivered to neonates if the ALKYMOS ACE filter was used.

RESULTS

The commercial Calcium Gluconate Injection, USP contained 3200 to 4500 mcg/L Al. More than 90% of the Al from 100 mL of this product was removed by the ALKYMOS ACE filter (Figure 1). When the Al concentration of Calcium Gluconate Injection, USP was 8000 or 11,500 mcg/L (after addition of Al nitrate), the filter still removed ≥85% of the Al (Figure 2). Al removal rates were 87% and 84% by 25- and 50-kGy gamma-sterilized filters, respectively. The calcium concentra-

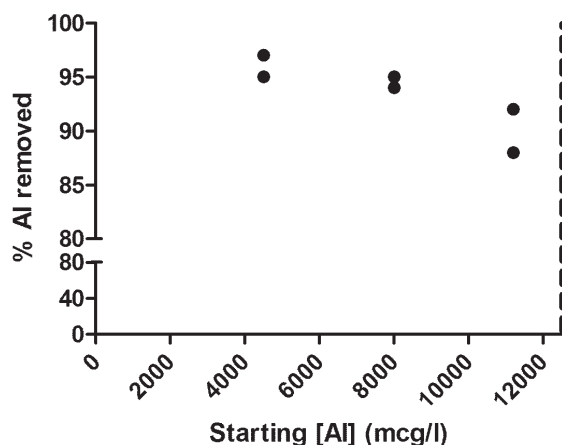


Figure 2. Percentage of aluminum (Al) removed from commercial Calcium Gluconate Injection, USP, to which Al was added, by the ALKYMOS ACE filter. Dashed vertical line is maximum commercial product Al concentration. Results are the 2 replicates at each concentration.

tions after filtration through filters exposed to 25- and 50-kGy gamma irradiation were 100% and 101%, respectively. Assuming removal of 85% of the Al from calcium gluconate, which is contributing 85% of the Al in prepared PN solutions,^{15–18} we calculate that the ALKYMOS ACE filter should reduce Al in the PN solution by 72%.

Two examples illustrate the amount of Al that can be removed using the ALKYMOS ACE filter. Among infants weighing between 1 and 6 kg in the Poole et al¹³ study, those weighing 1 to 2 kg were exposed to the highest average Al load (17.62 mcg/kg/day). Using the ALKYMOS ACE filter, which should reduce Al by 72%, the daily Al exposure would be 4.9 mcg/kg/day (Figure 3). For infants weighing less than 1 kg, Poole et al¹³ reported Al exposure of 23.11 mcg/kg/day. After calcium gluconate filtration, Al load should be reduced to 6.4 mcg/kg/day. So this filtration system will allow for daily Al delivery below the level that results in Al accumulation associated with central nervous system and bone toxicity, except for those infants who weigh less than 1 kg or who have an extraordinarily high calcium requirement.

DISCUSSION

Several concepts were considered and investigated to remove Al from Calcium Gluconate Injection, USP using an immobilized chelator (resin). Numerous prototypes were tested to de-

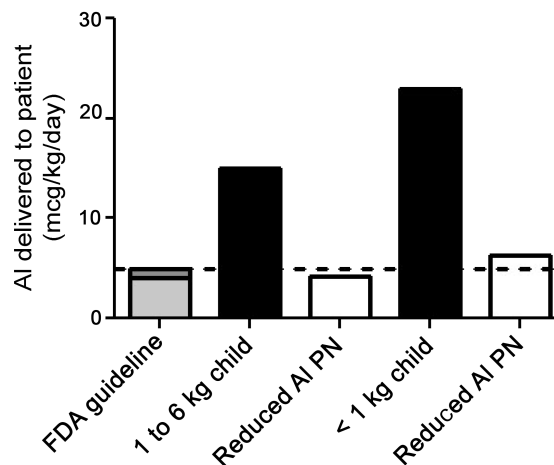


Figure 3. Predicted aluminum (Al) in PN solutions prepared with ALKYMOS ACE-filtered calcium gluconate. Al delivered daily to patients by parenteral nutrition (PN) from Poole et al¹³ (black filled histograms) and the calculated daily Al load, assuming that calcium gluconate contributes 85% of the total Al to PN and that 85% of the Al from calcium gluconate is removed by filtration through the ALKYMOS ACE filter (open histograms), compared with the 5 mcg/kg/day Food and Drug Administration guideline (horizontal dashed line).

termine the influence of flow rate, concept, and calcium gluconate Al concentration on Al extraction. A filter containing the resin through which Calcium Gluconate Injection, USP was drawn showed the greatest reduction of Al, >90%. Filters sterilized by gamma irradiation removed 85% of the Al. This process required no auxiliary equipment and was completed in less than 2 hours.

This approach has the potential to address the long-standing concern regarding the amount of Al delivered in PN solutions, particularly to premature neonates. This approach focuses on reduction of Al in the primary source contributing Al to PN solutions, Calcium Gluconate Injection, USP. Premature neonates are at greatest risk of Al accumulation and potential toxicity because of their incompletely developed renal function and high calcium requirement. This long-recognized problem has not been adequately resolved. In 1986 an FDA Advisory Panel recommended that Al be eliminated from components of PN solutions.³⁰ After three open meetings to discuss this issue,³¹ the FDA published in 1990 a Notice of Intent to establish a labeling requirement. In 1998, the FDA proposed a rule, "Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition," to amend its label-

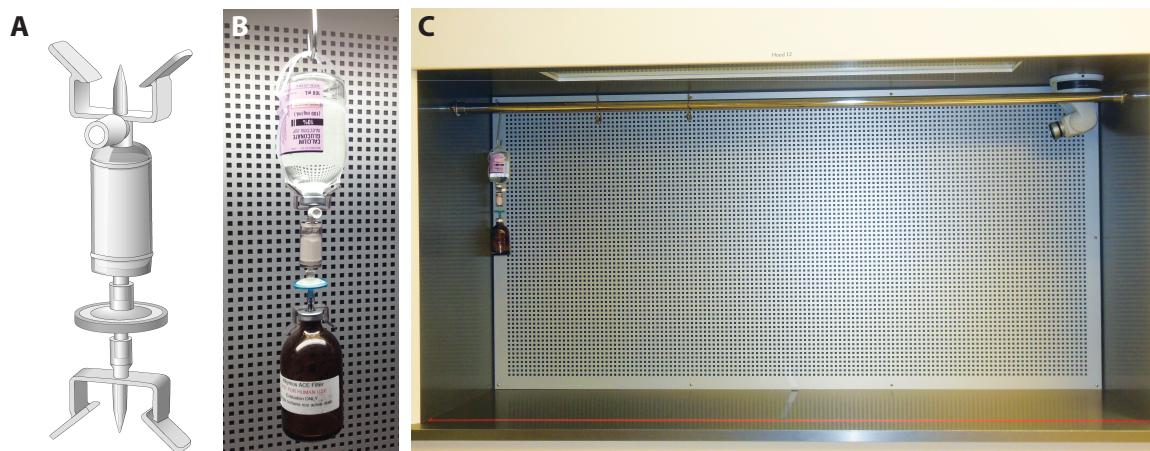


Figure 4. (A) A schematic diagram of the ALKYMOS ACE filter. (B) The ALKYMOS ACE filter system and a commercial vial of Calcium Gluconate Injection, USP during filtration of the calcium gluconate solution. (C) The ALKYMOS ACE filter system and a commercial vial of Calcium Gluconate Injection, USP during filtration, to illustrate the space requirement for this process.

ing requirement. The rule noted that “levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate with central nervous system and bone toxicity,”³² set an upper limit of 25 mcg/L (0.90 μ M) of Al in LVPs used in PN, and required a statement of the maximum Al concentration in SVPs at expiry. The information was intended to allow health care professionals to calculate a patient’s exposure to Al when receiving PN and to take actions that limit intake in patients susceptible to Al toxicity. After 3 delays, the rule was implemented on July 26, 2004, as 21CFR(201.323), and was updated in 2012.¹⁴ The delays were due to concerns expressed by SVP manufacturers that they were probably not meeting the limit and that it may be difficult to do so.³³ The Al content of PN solutions still exceeds the FDA safe level.^{12,13} Furthermore, the Al content of PN solutions cannot be accurately determined by calculation based on the maximum Al content of components used to compound the PN solution.¹³ Calcium gluconate solution Al content increases over time when it is stored in a glass vial, because of leaching of Al from the glass.¹⁹ This increase was observed during conduct of the present study. Therefore, a statement of Al content in Calcium Gluconate Injection, USP at the time of release, as suggested,²⁶ would not provide information about the Al concentration at the time of use. Because it is not practical to routinely quantify Al in prepared PN solutions, or even Calcium Gluconate Injection, USP prior to PN administration, health care professionals are delivering an

unknown amount of Al to their patients.

It was suggested to add desferrioxamine to PN solutions to complex the Al as aluminoxamine, which would presumably be eliminated in the urine, assuming adequate renal function to do so.³⁴ However, this would potentially expose the patient to desferrioxamine, which has considerable adverse effects. Desferrioxamine complexes trivalent metals and forms a stronger coordination bond with iron than Al,³⁵ potentially reducing iron and other essential metals. The present approach uses the same functional group as desferrioxamine (hydroxamic acid) to remove the Al before it enters the PN solution.

CONCLUSIONS

The ACE filter, developed by ALKYMOS, draws Calcium Gluconate Injection, USP from the commercial SVP vial through a cartridge containing hydroxamic acid-containing resin into an evacuated receiving vial. The low-Al calcium gluconate solution from the receiving vial would then be used to prepare PN solutions. The Al removal process is conducted off-line and can be initiated prior to PN preparation so that it does not interfere with or have a direct impact on PN preparation, and the filtered calcium gluconate is ready to use when PN compounding begins. This pharmaceutical compounding process takes 2 hours. Multiple vials can be filtered simultaneously. The space required is quite small and is above the working counter of the laminar flow

hood, so that multiple filtration systems could be operating while other activities are ongoing in the laminar flow hood (Figure 4). The filtration process should be initiated at the onset of PN preparation setup so that the filtered calcium gluconate solution will be available 2 hours later when PN preparation begins.

The ALKYMOS ACE filter is a point-of-use, self-contained, single-use, disposable, Al-complexing filter. It has been shown to remove 85% of the Al from Calcium Gluconate Injection, USP. It should reduce Al delivered in PN solutions by 72%, resulting in daily Al delivery below the level considered toxic to all but the smallest (<1 kg) infants. This filter system fills a void because currently there are no commercially available options to reduce Al for the pharmacist to employ to extract Al from pediatric and neonatal PN.

Disclosure Robert A. Yokel, Wesley R. Harris, Christopher D. Spilling, and Robert J. Kuhn are ALKYMOS shareholders. Robert A. Yokel has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Abbreviations Al, aluminum; FDA, Food and Drug Administration; LVP, large volume parenteral; PN, parenteral nutrition; SVP, small volume parenteral; USP, US Pharmacopeia

Correspondence Robert A. Yokel, PhD, Department of Pharmaceutical Sciences, 335 Biopharmaceutical Complex (College of Pharmacy) Building, College of Pharmacy, University of Kentucky Academic Medical Center, Lexington, KY 40536-0596, email: ryokel@email.uky.edu

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