Letter to the Editor

Parenteral Calcium Gluconate Supplementation: Efficacious or Potentially Disastrous?

We read with interest the recent article describing computer software assisted ordering (CSAO) of calcium and phosphorus in parenteral nutrition (PN) solutions [1]. There are several points in our opinion that deserve further clarification prior to implementation of such a CSAO system.

To our knowledge, there have been 9 published articles specifically focusing on the compatibility issues between calcium and phosphate in PN solutions (not necessarily all in neonatal populations) [2–10]. Visual analysis for "suspected" calcium-phosphate precipitates is a common method used in these types of studies [2–10]. Many have also utilized microscopic analysis after filtration [4–6,8] or a spectrophotometer [3,9] to evaluate for precipitates in solutions consisting of various dextrose and amino acid concentrations. Porcelli and Block [1] described the use of a positioned flood light to evaluate for crystallization of the complex CSAO solutions. Technical advances in compounding equipment has unfortunately predated the development of more sophisticated and practical methods for detection of precipitate formation in these complex solutions. The unaided human eye cannot see particles $<50\ \mu$ and they may be potentially hazardous if infused. Most neonatal intensive care units hopefully use $0.22\ \mu$ in-line filters to avoid infusions of particles $>6\ \mu$, which may occlude pulmonary capillaries. There was no mention of whether the flood light was used to evaluate for crystallization after the CSAO PN solutions were infused for 18–24 hours in the neonatal intensive care unit. Most cases of crystallization do not occur immediately after compounding, however, this is also a temperature-dependent variable. The influence of clinical conditions, such as an incubator, may increase the temperature of the PN solution and risk of precipitation [9].

One of the major disadvantages to many of the previously mentioned compatibility studies has been the omission of magnesium. The addition of magnesium may further influence the interaction between calcium and phosphate [11]. Porcelli and Block [1] described how calcium and phosphate doses were calculated after the amount of magnesium was specified. The calcium and phosphorus compatibility curve published in their manuscript has no designation of magnesium concentration used. Their compatibility curve also does not specify which amino acid formulation was used (although TrophAmine® 10% was mentioned elsewhere) or the dextrose concentrations used. The calcium-phosphate solubility variation previously seen in other studies with dextrose concentrations of 10–25% and amino acid concentrations of 0.4–4% requires specific information to understand what type of solutions may be used with a given concentration of calcium or phosphate. Publishing solubility curves for calcium and phosphate should follow the examples of previous authors with specific information to prevent inappropriate clinical application and potential patient harm.

Cysteine has been used to decrease the pH of the PN solution and increase calcium-phosphate solubility for neonates. Porcelli and Block [1] used 40 mg of cysteine per gram of amino acid used (standard dose used in the literature) to accomplish a lower pH, although specific pH values of their PN solutions were not reported. The pH of L-cysteine hydrochloride is typically between 1.0–2.5. However, the authors have incorporated an unusual combination to their PN formulations. One of the printed computer screens in their CSAO program asks if sodium acetate can be added to the PN solution, otherwise it will be added as sodium bicarbonate. Sodium bicarbonate has a pH of 7.0–8.5, which may increase the final pH of the PN solution if enough is added. At higher pH values, calcium and phosphate are less soluble and may precipitate. This may also neutralize the pH-lowering effect of cysteine. Sodium bicarbonate may also dissociate and react with calcium gluconate to form calcium carbonate, which is practically insoluble. More importantly, the order of mixing of PN additives, such as sodium bicarbonate, cysteine, calcium gluconate, and phosphate salts to the final PN solution becomes critical.

Although the CSAO program deserves credit for increasing calcium and phosphate intake in this patient population, the safety of such a program deserves further study. Data regarding clinical outcomes and the optimal calcium to phosphate ratio also remain undefined in very-low-birth-weight infants (Ca: PO_4 ratio of 1.8:1 was used). Merely providing more calcium and phosphate with PN solutions does not necessarily translate into providing improved clinical outcomes for patients, especially considering the aluminum contamination of PN solutions containing calcium gluconate. There has only been one publication regarding calcium and phosphate solubility which utilized calcium chloride (much lower aluminum contamination

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potential) [2]. This PN study, which supported the use of calcium gluconate with phosphate salts typically used in the U.S., found a lower degree of dissociation with higher concentrations of calcium gluconate as compared to calcium chloride.

A recent publication has shown PN solutions prepared with calcium gluconate contributes to impaired neurologic development primarily from aluminum contamination in premature infants [12]. Based upon these results, we should be providing adequate calcium and phosphate supplementation with minimal aluminum contamination of the PN solution. Until commercial organic phosphate solutions are available in the U.S., we should be promoting the development of PN compatibility curves for inorganic phosphate salts and calcium chloride (or other calcium salts) with less aluminum contamination to provide safe nutrition for these infants. However, the clinical application of any computerized system for ordering specialized nutrition support should be rigorously evaluated for safety and efficacy before widespread use.

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Author's Reply

We thank Drs. Canada and Albrecht for their thoughtful comments. We would like to preface our reply by noting that we did this work primarily to illustrate the successful implementation of decision support software to aid design of parenteral nutrition in the intensive care nursery. We used calcium: phosphorus (Ca:P) solubility to demonstrate that decision support software is capable of enhancing provision of these elements by relying on a complex formula beyond the usual scope of parenteral nutrition ordering systems [1]. Nevertheless, we also recognize the need to critique and modify infant nutrition with the goal of improving survival and outcome, and acknowledge Drs. Canada and Albrecht's concern about the potential toxicity of aluminum from commercially available calcium gluconate sources.

Drs. Canada and Albrecht asked whether Ca:P precipitates were specifically sought and whether we use inline filters during the infusion of parenteral nutrition. Our pharmacists use floodlights with a solid background at the time of admixing to detect precipitation. Furthermore, nursing staff visually inspect the parenteral nutrition bag at regular intervals before and during infusion. This approach is used at many nurseries. We have not detected precipitation in the solution using the decision support software nor are aware of complications secondary to precipitation in the patients. We recommend utilizing a filter system if there is a concern about precipitation, as we do in our unit. We stress that the design of our solution should minimize the formation of crystals, since the solubility is addressed during the design stage of parenteral nutrition fluid. We recognize that Ca:P precipitation may occur throughout the 24-hour infusion, though our experience is that most parenteral nutrition Ca:P precipitation occurs within a short period after the solution is prepared.

Drs. Canada and Albrecht also requested information regarding the parenteral nutrition components dextrose, trophamine and magnesium, and information describing parenteral nutrition magnesium content. Dextrose is provided as D70W (70 grams/100 mL, Abbott Laboratories, Chicago IL). Trophamine is provided as the 10% concentration (10 grams/100 mL, McGaw Inc, Irvine CA), and magnesium is provided as MgSO4 (50 mg/100 mL, American Regent, Shirley, NY). Solubility data for Trophamine was provided by McGaw Inc. With respect to parenteral nutrition magnesium content, we reviewed the 6239 parenteral nutrition records prepared at

Brenner Children's Hospital between 01/01/1996 and 12/31/1997. The average magnesium concentration was 28.3±13.3 mg/mL (mean±1 SD). We concur that further Ca:P solubility information for clinicians to design parenteral nutrition must continually be reevaluated as the field of neonatal parenteral nutrition develops.

Drs. Canada and Albrecht also correctly indicated that Ca:P precipitation is a function of several mixture factors: time, temperature and solution pH in addition to calcium and phosphorus concentrations [2–4]. The use of cysteine HCl to decrease pH and increase Ca:P solubility has been described and is applied in *Neohal,* our decision support software [5,6]. Acetate is always identified as the default base. Sodium bicarbonate is rarely used and must be specifically ordered in *Neohal.* Its use is indicated only when the infant has such severe hepatic failure that the ability to convert acetate to bicarbonate is significantly impaired. The *Neohal* manual cautions that "If acetate is rejected, sodium bicarbonate is used as the remaining anion source. This may result in higher solution pH and decrease calcium/phosphorus solubility."

Neohal was developed as an aid to design neonatal parenteral nutrition. It is not a replacement for a knowledgeable, conscientious medical care provider. The instruction manual stresses the importance of careful review of the orders produced by the software and that *Neohal* is a tool to facilitate the design of parenteral nutrition, not a substitute for the medical care provider to make clinical nutrition decisions.

Drs. Canada and Albrecht note that no clinical improvement was described using the software. This is true since our paper described the efficacy of the program as a decision support tool to design neonatal parenteral nutrition. The study was not intended to answer questions of clinical improvement or long-term outcome. Other investigators have described optimal parenteral calcium and phosphorus administration via parenteral nutrition [7,8].

Last, Drs. Canada and Albrecht note the recent report describing neurodevelopmental differences of preterm infants as a function of aluminum intake [9]. This report raises concern for aluminum intake via parenteral nutrition in preterm infants. Given that the calcium gluconate component of parenteral nutrition provides a significant amount of the aluminum found in parenteral nutrition, techniques to reduce parenteral nutrition aluminum content must be investigated.

There are several options for decreasing the aluminum load. Industrial producers can be encouraged to monitor and decrease the aluminum load during production. This may be costly and, given the small quantities needed annually for this purpose, the manufacturers may be reluctant to invest large sums in reformulation, solubility analysis and monitoring. Alternatives to calcium gluconate can be sought. The use of calcium chloride produces a separate set of concerns, including additional provision of chloride, its effect on the pH of the solution, parenteral nutrition solubility issues, and contamination with aluminum. A third alternative would be the use of a compound such calcium glycerophosphate which contains chemically bound calcium and phosphorus designed to prevent large precipitate salts from forming in vitro. It has been available in Europe for several years and has been investigated for use in Canada. This compound offers the safety of solubility in solution; however, we are unaware whether the aluminum content of this compound has been described. In addition, it is not currently approved for use in the United States.

In summary, Drs. Canada and Albrecht raise several important issues, and we share many of their concerns, especially regarding aluminum. We hope that this issue will continue to receive ample attention from both academic investigators and industry.

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