Maximizing Calcium and Phosphate Content in Neonatal Parenteral Nutrition Solutions Using Organic Calcium and Phosphate Salts

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Precipitation of calcium phosphate is the most important physical incompatibility in parenteral nutrition (PN), particularly for preterm infants who require high concentrations of these electrolytes. Indeed, premature neonates have very high calcium (Ca) and phosphate (PO₄) requirements for bone mineralization and are often restricted in fluid intake. Ca and PO₄ tend to form an insoluble precipitate that may result in catheter occlusion or more serious clinical complications such as microvascular pulmonary emboli.¹

Factors affecting calcium phosphate solubility include concentrations of the 2 electrolytes, composition and concentration of amino acids and glucose, temperature, pH of the final solution, presence of other electrolytes, length of storage, nature of salts used (inorganic or organic Ca and PO₄ salts), and order of mixing.² ⁴ The nature of Ca and PO₄ salts directly influences the solubility of calcium phosphate. Given the differences in dissociation characteristics, the relative concentrations of Ca or PO₄ available for precipitation are higher when inorganic salts are used. Organic Ca salts such as calcium glutionate (Ca-glu) are widely used, whereas the availability of organic PO₄ salts such as sodium glucose-1-phosphate (G1P) or sodium glycerophosphate is more limited because they are not registered and approved for use in every country.

Since 2001, pediatric PN has been prescribed in our institution with an integrated software developed to provide, guide, and promote safety limits to the prescribing physician. At the time the software was implemented, Ca-glu injection and an admixture of sodium and potassium PO₄ were used to produce PN. In accordance with the precipitation curve described by Henry et al,⁵ Ca and PO₄ concentrations in our PN admixtures were limited to a maximum of 5 mmol/L. In 2005, the inorganic phosphate salts were replaced by G1P in our institution. Different studies have shown that higher amounts of Ca and PO₄ organic salts could be mixed without precipitation. These studies were performed in definite standard PN solutions, differing from the PN solutions produced in our institution, which cover a wide range of concentrations.

**Background:** The provision of high amounts of calcium and phosphate in parenteral nutrition (PN) solution for neonates is important for bone mass accretion. Because of the risk of calcium phosphate precipitation, a well-documented incompatibility for inorganic salts, the concentrations of these electrolytes in PN are generally limited to 5 mmol/L. The aim of this study was to assess the risk of precipitation of calcium phosphate when organic calcium and phosphate salts are used instead of inorganic salts. **Methods:** Precipitation curves were determined for inorganic and organic calcium and phosphate salts in a PN solution favorable to precipitation (low concentration of amino acids and glucose) using visual inspection and particle counts.

**Results:** The use of organic phosphate salt was associated with a decreased risk of precipitation of calcium phosphate. No precipitation occurred up to a concentration of 50 mmol/L of calcium and phosphate. In contrast, organic calcium salt only slightly decreased the risk of precipitation. **Conclusion:** Up to 50 mmol/L of organic calcium and phosphate salts can be safely mixed in PN, even in unstable conditions, making it possible to follow the current European recommendations for requirements in neonates. (JPEN J Parenter Enteral Nutr. 2010;34:542-545)

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of each nutrient. At this time, we decided not to increase limits of prescription for Ca and PO₄ until a structured evaluation of the risk in our usual conditions was conducted.

The ESPGHAN/ESPEN guidelines recommend the administration of 1.3–3 mmol/kg/d of Ca and 1–2.3 mmol/kg/d of PO₄ for growing newborn infants. Unfortunately, these requirements are seldom met in our institution because of the limits imposed in prescribing Ca and PO₄. On average, the prescriptions of Ca and PO₄ are, respectively, 0.6 ± 0.4 mmol/kg/d and 0.7 ± 0.4 mmol/kg/d for low birth weight infants (internal data). It seems therefore important to increase Ca and PO₄ amounts in PN for our neonates.

The aim of this study was to assess the risk of precipitation when high concentrations of Ca and PO₄ organic salts are mixed in a formulation with high risk of instability. The goal was to safely increase the limits of Ca and PO₄ in our electronic prescription software, thereby permitting better compliance with international recommendations.

### Methods

A PN mixture that was favorable to precipitation was determined (Table 1) based on a retrospective analysis of the PN prescriptions made between 2003 and 2006 in the neonatal and pediatric intensive care units of our hospital. The lowest concentrations of glucose and amino acids were chosen at 3% and 0.4%, respectively, because they are more favorable to calcium phosphate precipitation. Average concentrations of electrolytes, trace elements, and heparin were used. Acetate, which was seldom prescribed, and magnesium were not included in the tested PN admixtures. Magnesium sulfate was not included because the concentrations of this electrolyte used in our PN solutions are too low to form a calcium sulfate precipitate. Two calcium and 2 phosphate salts were tested (Table 1).

All PN solutions were aseptically prepared in a class A horizontal laminar-airflow hood, located in a GMP class B clean room, with the help of an automated compounding machine (BAXA MM12).

To simulate clinical conditions, all samples were stored for 48 hours at 4°C and for 24 hours at 32°C prior to analysis. At the end of the storage period, the samples were visually inspected against a black-and-white contrast background for evidence of precipitation. Particles were counted in clear samples (after the samples were gently mixed to ensure that no particles adhered to the surface) as recommended by the European Pharmacopoeia (EP) with a Hiac/Royco 90/64 laser light extinction particle counter (Pacific Scientific, USA) placed in a horizontal laminar

### Table 1. Composition of the Raw Materials Used for the Parenteral Nutrition Solutions

<table>
<thead>
<tr>
<th>Additives</th>
<th>Products</th>
<th>Initial Concentrations</th>
<th>Manufacturer</th>
<th>Final Concentrations in Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>Vaminolact</td>
<td>6.53%</td>
<td>Fresenius Kabi, Stans, Switzerland</td>
<td>0.4%</td>
</tr>
<tr>
<td>Dextrose</td>
<td>Dextrose 70%</td>
<td>70%</td>
<td>Fresenius Kabi, Stans, Switzerland</td>
<td>3%</td>
</tr>
<tr>
<td>Sodium</td>
<td>NaCl 11.7%</td>
<td>Na, 2 mmol/mL</td>
<td>Bichsel, Interlaken, Switzerland</td>
<td>80 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>KCl 7.5%</td>
<td>K, 1 mmol/mL</td>
<td>Sintetica-Bioren, Couvet, Switzerland</td>
<td>30 mmol/L</td>
</tr>
<tr>
<td>Trace elements</td>
<td>Tracutil</td>
<td>800 mcg/mL</td>
<td>BBraun, Sempach, Switzerland</td>
<td>2400 mcg/mL</td>
</tr>
<tr>
<td>Heparin</td>
<td>Heparin 50 international units/mL</td>
<td>50 international units/mL</td>
<td>Internal production</td>
<td>0.5 international units/mL</td>
</tr>
<tr>
<td>Inorganic calcium</td>
<td>Calcium chloride (CaCl₂)</td>
<td>Ca, 0.16 mmol/mL</td>
<td>Fagron, Colombes, France</td>
<td>Variable</td>
</tr>
<tr>
<td>Organic calcium</td>
<td>Calcium glutionate (Ca-glu)</td>
<td>Ca, 0.16 mmol/mL</td>
<td>Bichsel, Interlaken, France</td>
<td>Variable</td>
</tr>
<tr>
<td>Inorganic phosphate</td>
<td>Dibasic sodium phosphate (Na₂HPO₄)</td>
<td>PO₄, 0.33 mmol/mL; Na, 0.66 mmol/mL</td>
<td>Hänseler, Herisau, Switzerland</td>
<td>Variable</td>
</tr>
<tr>
<td>Organic phosphate</td>
<td>Disodic glucose-1-phosphate (G1P) (Phocytan)</td>
<td>PO₄, 0.33 mmol/mL; Na, 0.66 mmol/mL</td>
<td>Aguettant, Lyon, France</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*Fe 195 mcg/mL, Zn 327 mcg/mL, Mn 55 mcg/mL, Cu 76 mcg/mL, Cr 1 mcg/mL, Mo 1 mcg/mL, Se 2 mcg/mL, F 57 mcg/mL, I 13 mcg/mL, Na 71 mcg/mL, K 3 mcg/mL
airflow hood to avoid particle contamination. Particle counts were assessed by a mean of 4 counts of 10 mL of PN solution for each sample. The solutions fulfilled the EP limits when no more than 25 particles ≥10 µm/mL and 3 particles ≥25 µm/mL were determined. Measurements of pH were performed using a validated pH meter (Mettler Toledo GmbH, Switzerland).

Results were classified in 3 categories according to the results: “stability zone” for clear samples and particle counts within the EP limits, “intermediate zone” for clear samples but number of particles above the EP limits, and “precipitation zone” when visible particles or precipitates were detected.

Calcium phosphate precipitation curves were established by increasing step by step quantities of calcium and phosphate in the 4 different combinations in a concentrations ranging from 1 to 50 mmol/L. When inorganic phosphate salt was used, concentrations were increased by steps of 1 mmol/L for each salt (Ca and PO₄), beginning at 1 mmol/L and continuing to 12 mmol/L. When particles counts of samples were in the intermediate zone, 2 more steps at ±0.5 mmol/L were added to refine the curve. When organic phosphate salt was used, steps between 2 concentrations were 10 mmol/L of each salt, beginning at 10 mmol/L and continuing to 50 mmol/L.

Results

Precipitation occurred at low concentrations of calcium and phosphate when inorganic salts were used in studied PN admixtures (Figure 1a). Precipitation appeared immediately on mixing or developed during the storage period. The pH of the PN solutions remained stable in all samples between 4.9 and 6.9.

The combination of Na₂HPO₄ and Ca-glu instead of CaCl₂ in studied PN admixtures allowed an increase of only 1–2 mmol/L of these electrolytes concentrations without any precipitation (Figure 1b) compared with the combination of both inorganic salts. The pH of all samples was between 6 and 7.2.

When G1P was used, associated with CaCl₂ or the organic calcium, concentrations of each electrolyte could be increased up to 50 mmol/L without any precipitation (Figure 1c). Solutions with organic phosphate never presented a precipitate or a number of particles above the EP limits. The pH of all samples was between 5 and 7.5, the highest pH corresponding to solutions with the highest amount of PO₄.

Discussion

Maximizing Ca and PO₄ concentrations without increasing the risk of precipitation is an ongoing challenge in the manufacturing of PN solutions, particularly in the neonatal population. In this study, we have provided experimental information useful to optimize the manufacturing of PN solutions containing calcium and phosphate. Although different studies pointed out that the solubility of calcium phosphate depends on several variables such as pH or concentration of amino acids and glucose,² ⁴ ⁷ this study demonstrates that the most relevant factor is the nature of the salt. Moreover, organic PO₄ salt provided the greatest

Figure 1. Precipitation curves with inorganic and organic calcium and phosphate salts.
benefit over organic Ca salt to avoid calcium phosphate precipitation. When G1P was used, solutions remained clear with particle counts within EP limits after addition of either CaCl₂ or Ca-glu. When Na₂PO₄ was used, concentration of Ca without precipitation was increased only 1–2 mmol/L with Ca-glu instead of CaCl₂.

To the best of our knowledge, this study is the first performed in conditions particularly prone to precipitation (low concentration of amino acids and glucose) and not in usual PN (usual concentrations of amino acids [2%–4%] and glucose [8%–12%]). Our data provide evidence that even in these worst-case conditions, a wide range of PN admixtures with up to 50 mmol/L of Ca-glu and G1P are stable for 2 days at 4°C, followed by 1 day at 32°C, a value corresponding to the ambient temperature in a neonatology unit. Consequently, limits included in our prescribing software were increased, allowing the prescription of Ca and PO₄ up to 50 mmol/L for each electrolyte. Physicians are no longer limited in Ca and PO₄ prescription and are able to follow the current European guidelines for neonates.

Given that organic salts of Ca and PO₄ are 5–10 times more expensive than inorganic salts, the combination of organic PO₄ salts with CaCl₂ would be economically advantageous. However, CaCl₂ is completely dissociated in aqueous solution, and high concentration of divalent cations could be detrimental to the stability of the lipid emulsion administered simultaneously at Y-site injection. The use of Ca-glu thus retains its interest in PN admixtures containing organic calcium and inorganic phosphate salts.

In conclusion, the use of Ca and PO₄ organic salts overcome the problem of precipitation up to a concentration of 50 mmol/L of each mineral in a wide range of PN solutions even in the worst-case situations. The allowed concentrations of Ca and PO₄ in the PN for premature infants could be increased by a factor of 10 compared with the limits in use prior to this study. Current European recommendations for neonates regarding the amounts of Ca and PO₄ in PN can be followed safely when using organic salts without risk of calcium phosphate precipitation.

References