Are there maximum compatible concentrations of calcium gluconate and sodium glycerophosphate in infant parenteral nutrition solutions?

Nattaphorn Thowladda¹, Tippawan Siritientong¹*
¹ Department of Food and Pharmaceutical Chemistry, Faculty of Pharmaceutical Science, Chulalongkorn University, Bangkok 10330, Thailand.

Abstract

Background: Calcium gluconate and sodium glycerophosphate (NaGP) were claimed to reduce risk of precipitation in infant parenteral nutrition (PN) solutions which contained high amounts of calcium and phosphorus.

Objective: To determine the compatibility of calcium gluconate and NaGP at high concentrations in PN solutions with different amino acid concentrations and storage conditions.

Methods: PN solutions consisted of 1.5-2.5% amino acid, 0-100 mM/l calcium gluconate and 0-150 mM/l NaGP in constant amounts of dextrose, sodium chloride, and magnesium sulfate. The solutions were kept under 3 conditions; 30°C for 1 d, 4°C for 1 d and 4°C for 7 d. Compatibility initially evaluated by pH measurement and visual inspection. Solutions were then measured turbidity and further observed under a light microscope for microscopic particle count test. PN solution was determined to be compatible if particle counts of three replicates were under USP criteria.

Results: PN solutions containing 1.5% and 2.0% amino acid with high concentrations of calcium gluconate and NaGP showed precipitation. Fifty mM/l calcium gluconate was compatible with 150 mM/l NaGP as freshly prepared and 100 mM/l NaGP as kept in 30°C for 1 d, respectively. At any storage conditions of solutions containing 2.5% amino acid, 75 mM/l of calcium gluconate was compatible with 100 mM/l NaGP.

Conclusion: The use of calcium gluconate and NaGP in PN solutions allowed high compatible concentrations of calcium and phosphorus. These organic salts should feasibly be applied in prescription and compounding of infant PN solutions.

Keywords: calcium, compatible, phosphate, parenteral nutrition, sodium glycerophosphate

INTRODUCTION

Premature infants have high requirement of calcium and phosphorus due to lack of calcium-phosphorus accretion [1]. Parenteral nutrition (PN) providing to these patients always contained high amounts of calcium and phosphorus to prevent osteopenia and fractures [2]. High concentrations of these minerals in the infant PN solutions lead to form calcium-phosphate precipitates. In addition to mineral concentrations, many factors influenced in calcium and phosphorus compatibility in PN solution including order of mixing, pH of the solution, concentration of amino acid, storage time, temperature and salt forms of minerals [3]. Organic salts of calcium and phosphate have been recently recommended to be used instead of inorganic salts to avoid calcium-phosphate precipitation in infant PN solutions [4-8]. Previous studies reported that sodium glycerophosphate (NaGP) at the concentration of 50 mM/l corresponding to calcium gluconate at the concentration of 25 mM/l showed no precipitation [9]. Organic phosphates at the concentration of 50 mM/l were compatible with either inorganic or organic calcium [4, 7]. A recent study had reported the compatibility of 30 mM/l calcium gluconate and 50 mM/l NaGP mixed with 2% amino acid (Aminoven infant 8) in PN solutions stored at 30°C for 1 day, 4°C for 1 day and 4°C for 7 days. In contrast, precipitations were obviously observed in PN solution containing calcium gluconate and inorganic phosphate 20 mM/l equally of each [10].

Although organic salts of calcium and phosphorus may offer improved mineral solubility, the saturation curves are still needed to eliminate the concern about precipitation of calcium gluconate and NaGP in PN solutions. This concern always occurs in patients with restricted fluid volume or patients who need high amounts of calcium and phosphorus especially preterm infants [11, 12]. The pediatricians may be doubtful to order and pharmacists may feel uncomfortable in PN compounding. There is still no conclusive evidence about the maximum concentrations of calcium gluconate and NaGP without precipitation in infant PN solutions. The aim of this study was to investigate the in vitro compatibility of calcium gluconate and NaGP in infant PN solutions according to various concentrations of amino acids, calcium gluconate, and NaGP. Effects of storage conditions on compatibility data were also evaluated.

MATERIAL AND METHODS

This is an experimental study. The retrospective review of infant PN solutions orders and pediatrician’s advices were gathered to identify appropriate PN formulas used in this study. The represented PN solutions consisted of 1.5, 2, and 2.5% amino acid, 0-100 mM/l calcium gluconate with each increment of 25 mM/l and 0-150 mM/l NaGP with each increment of 25 mM/l. All solutions contained constant amounts of dextrose, sodium chloride, and magnesium sulfate (Table 1). Maximum concentrations of calcium and NaGP used in this study were limited to 100 mM/l and 150 mM/l, respectively, due to limitation of commercial products concentrations and final total volume preparation of PN solution.

PN solutions were aseptically compounded in the laminar airflow hood. One-hundred ml of each PN formula was prepared in triplicate: Dextrose, amino acid, NaGP, sodium chloride, magnesium sulfate, were consecutively mixed after vigorous shaking at each step. Calcium gluconate was added lastly during the preparation. Each 25-ml admixture was separately stored according to 3 following storage conditions; 30°C for 1 d (simulated room temperature condition), 4°C for 1 d and 4°C for 7 d (simulated common storage conditions). All compatibility tests were done in triplicate in comparison to the freshly prepared solutions (control), including pH measurement, visual inspection, turbidity test and microscopic particle count test (Figure 1).

At the end of each storage time point, samples were measured pH and visual inspection against a black and white contrast background [13, 14]. The solutions with pH values less than 7.2 and no visible precipitate were then measured turbidity using a turbidimeter (HI 93414, Hanna Instruments, Italy) [6, 9, 14]. According to the United States Pharmacopeia (USP) 788 standards, the solutions with turbidity less than 0.5 nephelometric turbidity units (NTU) were then consecutively inspected under a light microscope (Nikon Eclipse E200, Inter Instrument.co., Ltd, Japan) for evidences of micro-precipitation under 10X magnification [14]. Five-ml aliquots of PN solution were
carefully filtered through a 0.45 μm cellulose nitrate membrane (Sartorius Stedim Biotech GmbH, Germany). The membrane was then observed for any microscopic particles. The maximum numbers of microscopic particles containing less than 60 particles measuring 10 μm in diameter together with less than 10 particles measuring 25 μm in diameter were considered as physically compatible [14]. All results were gathered to construct compatibility data of calcium gluconate and NaGP which classified into three zone; green zone = physically compatible, red zone = incompatible at any steps of the tests, grey zone = concentration point that cannot be prepared due to limitation of commercial products concentrations.

**Figure 1** Experimental design of the study
Table 1 Composition of raw materials used for the PN solutions

<table>
<thead>
<tr>
<th>Additives</th>
<th>Products</th>
<th>Manufacturer</th>
<th>Final Concentrations in Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose</td>
<td>50% Dextrose in water</td>
<td>General Hospital Products Public Co., Ltd., Thailand</td>
<td>10%</td>
</tr>
<tr>
<td>Sodium and chloride</td>
<td>3% Sodium chloride</td>
<td>General Hospital Products Public Co., Ltd., Thailand</td>
<td>51.3 mM/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>50% Magnesium sulfate</td>
<td>Atlantic Laboratories, Thailand</td>
<td>2.025 mM/L</td>
</tr>
<tr>
<td>Amino acids</td>
<td>10% Aminoven infant®</td>
<td>Fresenius Kabi, Austria</td>
<td>1.5, 2, and 2.5%</td>
</tr>
<tr>
<td>Organic calcium</td>
<td>10% Calcium gluconate</td>
<td>The Government Pharmaceutical Organization, Thailand</td>
<td>0-100 mM/L</td>
</tr>
<tr>
<td>Organic phosphate</td>
<td>Glycophos®</td>
<td>Fresenius Kabi, Austria</td>
<td>0-150 mM/L</td>
</tr>
</tbody>
</table>

RESULTS

Total ninety-one PN formulas were compounded, evaluated for pH measurement and visual stability. The pH values of all studied solutions at any concentrations of calcium and NaGP were less than 7.2; however, this study found some concentrations of calcium gluconate and NaGP which showed precipitation by visual inspection, turbidity measurement and microscopic particle count test. PN solutions containing 1.5% and 2.0% amino acid with high concentrations of calcium gluconate and NaGP showed precipitation (red zone in Figure 2 and Figure 3). High storage temperature and long storage duration also increased the opportunity of precipitation. Considering PN solutions containing 1.5% amino acid, 50 mM/l calcium gluconate was compatible with 150 mM/l NaGP as freshly prepared. In contrast, the solutions kept in 30°C and 4°C for 1 d, 50 mM/l calcium gluconate was compatible with 100 mM/l NaGP (Figure 2B, 2C). Compatible NaGP concentration reduced to be 50 mM/l when kept PN solution at 4°C for 7 d (Figure 2D). Similarly, considering PN solutions containing 2% amino acid, 50 mM/l calcium gluconate was compatible with 150 mM/l NaGP as freshly prepared and 4°C for 1 d (Figure 3A, 3C). Compatible NaGP concentration reduced to be 100 mM/l NaGP when the solutions kept in 30°C for 1 d and 4°C for 7 days (Figure 3B, 3D). At any storage conditions of solutions containing 2.5% amino acid, 75 mM/l of calcium gluconate was compatible with 100 mM/l of NaGP (Figure 4). All studied PN solutions which had turbidity less than 0.5 NTU were also pass the microscopic particle count test; however, traces of microscopic particles were observed on the filter membranes at the lower numbers than the USP criteria.

![Figure 2](compatibility_data.png) Compatibility data of PN solutions containing 1.5% amino acid at (A) freshly prepared and stored at (B) 30°C for 1 d (C) 4°C for 1 d (D) 4°C for 7 d (green: physically compatible, red: incompatible, concentrations that can not be prepared)
Figure 3 Compatibility data of PN solutions containing 2% amino acid at (A) freshly prepared and stored at (B) 30°C for 1 d (C) 4°C for 1 d (D) 4°C for 7 d (physically compatible, incompatible, concentrations that can not be prepared)

DISCUSSION
The calcium phosphate incompatibility is a significant problem in infant PN solution. Low PN volume, low concentrations of amino acids and high amounts of calcium and phosphate result in calcium-phosphate precipitation in PN solution [3]. The clinical studies reported calcium-phosphate precipitates may cause microvascular pulmonary emboli, respiratory distress, and even death due to the smallest capillary blood vessels have diameter of approximately 4 μm [3]. Previous studies reported several attempts to reduce the risk of calcium-phosphate precipitation including separate time of mineral administration, decrease the administered mineral concentrations regarding the published compatibility curves, and use of parenteral organic minerals [3, 15]. According to the compatibility results of PN solutions, gluconate salt of calcium was significantly more soluble than chloride salt [8-9, 16-17]. Likewise, organic salts of phosphorus including sodium glucose-1-phosphate, sodium D-fructose 1, 6-diphosphate and NaGP allowed higher compatible calcium concentrations than sodium monohydrogen phosphate or dipotassium phosphate [4, 10, 16, 18-19]. Therefore, when the precipitation in PN solution is foreseen, inorganic salts of calcium and phosphate should be replaced with calcium gluconate and NaGP to avoid the occurrence of calcium and phosphorus precipitation.

Although organic salts were used, this study surprisingly found that the precipitation still occurred in the PN
solutions with some concentrations of calcium gluconate and NaGP. However, the concentrations of calcium gluconate and NaGP that showed incompatible were extremely higher than the requirement for preterm infants. The ESPGHAN recommends that growing newborn infants should receive calcium 1.3-3.0 mM/kg/day and phosphorus 1.0-2.3 mM/kg/day [20]. Therefore, as calculated on the normal infants’ weight, the probability of calcium and phosphorus precipitates when using calcium gluconate and NaGP are rare. Our findings were in agreement as calculated on the normal infants’ weight, the probability of calcium phosphate gluconate and NaGP are rare. Our findings were in agreement as calculated on the normal infants’ weight, the probability of calcium phosphate.

CONCLUSIONS

The PN solutions containing low concentrations of amino acid, high concentrations of calcium and phosphate and long storage duration enhanced risks of precipitation in PN solutions. This study reported maximum compatible concentrations of calcium gluconate and NaGP in PN solutions. The PN solutions containing 1.5% and 2% amino acid showed precipitation at high concentrations of calcium and phosphate. The PN solutions containing 2.5% amino acid passed all compatibility tests at studied concentrations of calcium gluconate and NaGP. Compatibility data from this study can be referable for prescription and preparation of infant PN solutions.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

REFERENCES


