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Compatibility of calcium and sodium glycerophosphate in parenteral nutrition solutions

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Objectives: Preterm infants need high amounts of calcium and phosphorus for bone mineralization and growth, which is difficult to obtain with parenteral feeding due to its low solubility. The purpose of this study was to test the compatibility of sodium glycerophosphate (NaGP) with calcium gluconate in pediatric parenteral nutrition (PN) solutions.
Methods: Ten PN admixtures formulas for neonatal use were aseptically prepared. Standard formula consisted of 10%dextrose and 2%amino acid according to Ramathibodi Hospital pediatric PN prescription. In this study, calcium at the concentrations of 0, 20, 30 mmol/L and phosphate at the concentrations of 0, 20, 50 mmol/L, were orderly mixed into the standard formula. Each admixture separately tested according to 4 following conditions; after mixing, 30°C for 1 day, 4°C for 1 day and 4°C for 7 days. Visual inspections against a black and white contrast background, pH evaluation, spectrophotometry at 600 nm and particle size measurement were examined in triplicate.
Results: All testing parameters showed that PN solutions mixed with NaGP did not have any precipitation over 7-day storage duration. On the other hand, samples containing 50 mmol/L of inorganic phosphate and 30 mmol/L of calcium gluconate or inorganic phosphate and calcium gluconate 20 mmol/L equally of each, precipitations were obviously observed in PN admixtures.
Conclusion: NaGP showed no precipitation at all concentrations in PN admixtures used in this study. NaGP may be a good choice of phosphate source in PN preparation. However, further study was required to assess the safety, efficiency and cost-effectiveness of using NaGP in pediatric PN solutions.

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Introduction

Preterm infants need high amounts of calcium and phosphorus for bone mineralization and preventing abnormal growth. Due to limitation of oral intake, preterm infants are necessary to get all nutrients including calcium and phosphate from parenteral nutrition (PN). Practical solubility factors relevant to the safe administration of calcium and phosphate are concerned. In case of high risk of precipitation, either calcium or phosphate concentration needs to be reduced leading inefficient mineral intake[1].
Several factors have been identified that affect the solubility of calcium and phosphate in PN solutions, including the amounts of calcium and phosphate added to the solutions, the form of calcium salt used, amino acid concentration, amino acid composition, pH, storage duration, storage temperature, and the order of mixing[2].
Currently, there is a new parenteral phosphate product available in the market named sodium glycerophosphate (NaGP). NaGP is an organic phosphate developed to increase solubility compared to inorganic phosphate even in a solution containing high concentration of calcium or high pH so that PN would be comfortably prepared. One milliliter of NaGP contains phosphate 1 mmol and sodium 2 mmol. The recommended dose per day for infants and newborns is equal to 1.0-1.5 mmol per 1 kg of body weight[3]. Although use of NaGP in PN preparation gradually expands, there is still no conclusive evidence about calcium and NaGP compatibility. Objective of this study is to test the compatibility of NaGP with calcium gluconate in pediatric PN solutions.

Materials and Methods

Preparation of the admixtures studies

Ten PN admixtures formulas for neonatal use were aseptically prepared under a laminar flow hood. Standard formula consisted of dextrose at the concentration of 10% (Dextrose 50% in water, Thai Otsuka Pharmaceutical Co.,Ltd., Thailand) and amino acid at the concentration of 2% (Aminoven infant® 10%, Fresenius Kabi, Austria) according to Ramathibodi Hospital pediatric PN formulation. In this study, calcium gluconate (The Government Pharmaceutical Organization, Thailand) at the concentrations of 0 and 30 mmol/L and dipotassium phosphate (Thai Otsuka Pharmaceutical Co.,Ltd., Thailand) or sodium glycerophosphate (Glycophos®, Fresenius Kabi, Austria) at the concentrations of 0 and 50 mmol/L, used calcium gluconate concentrations at 20 mmol/L and dipotassium phosphate or sodium glycerophosphate

concentrations at 20 mmol/L equally of each, were orderly mixed into the standard formula.

Physicochemical assessments

Each admixture separately tested according to 4 following conditions; after mixing, 30°C for 1 day, 4°C for 1 day and 4°C for 7 days. Visual inspection against a black and white contrast background was examined to detect any color change, precipitation, film formation and phase separation with 3-watt LED lamp 220-240 V at 4 inches from the light source.[4, 5] pH of the sample solution was measured using pH meter (Ultra Basic, Denver Instrument, USA). Samples were examined for light scattering by UV spectrophotometer (ThermoSpectronic, Becthai Bangkok Equipment & Chemical Co.,Ltd., Thailand) at 600 nm against sterile water for injection blank. An absorbance of greater than 0.06 was determined as the "arbitrary threshold for precipitation".[6] For particle size evaluation, one milliliter of each sample was analyzed using a laser instrument (Zetasizer Nano ZS, Malvern Instruments Ltd, DKSH, Thailand) to determine the hydrodynamic diameter of the particles in a given solution (the Z average particle size). An average particle size of greater than 4 µm was determined as the "arbitrary threshold for precipitation".[7]

Results

Visual inspection was evaluated any color change, precipitation, film formation and phase separation for 10 PN admixtures formulas over 7-day storage duration, as shown in table 1 and figure 1. There was no visual precipitation in all solutions containing NaGP. On the other hand, samples containing 50 mmol/L of inorganic phosphate and 30 mmol/L of calcium gluconate or inorganic phosphate and calcium gluconate 20 mmol/L equally of each, precipitations were observed in PN admixtures.

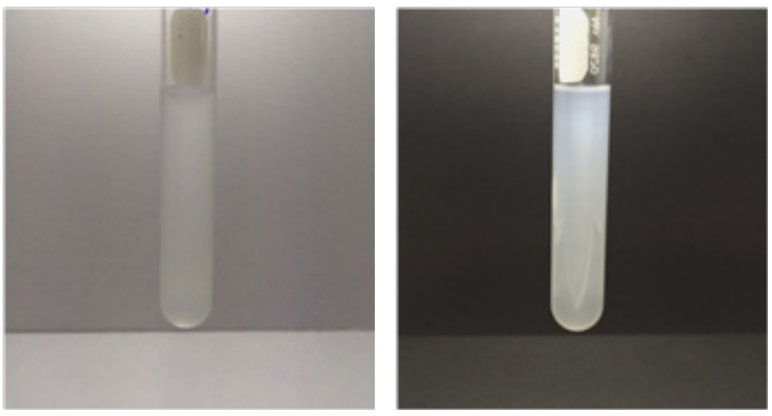
Table 2 showed means and standard deviations (SD) of pH values for PN admixtures during 7 days of study. In all cases, pH of the PN admixtures slightly increased regarding to longer storage duration.

Table 1. Visual inspection of PN admixtures

Types of phosphate	Concentrations (mmol/L)	after mixing	30 °C for 1 day	4 °C for 1 day	4 °C for 7 days
	Blank	✓	✓	✓	✓
	Ca 0 P 0	✓	✓	✓	✓
	Ca 0 P 50	✓	✓	✓	✓
Inorganic	Ca 20 P 20	×	×	×	×
	Ca 30 P 0	✓	✓	✓	✓
	Ca 30 P 50	×	×	×	×
	Ca 0 NaGP 0	✓	✓	✓	✓
	Ca 0 NaGP 50	✓	✓	✓	✓
NaGP	Ca 20 NaGP 20	✓	✓	✓	✓
	Ca 30 NaGP 0	✓	✓	✓	✓
	Ca 30 NaGP 50	✓	✓	✓	✓

✓ No precipitation × Precipitation,
Ca = Concentration of calcium gluconate (mmol/L), P = Concentration of dipotassium phosphate (mmol/L),
NaGP = Concentration of sodium glycerophosphate (mmol/L)

(a)



(b)

Figure 1. Visual inspection after mixing 30 mmol/L of calcium gluconate with (a) 50 mmol/L of dipotassium phosphate or (b) 50 mmol/L of sodium glycerophosphate

Table 2. pH values of PN admixtures

Types of phosphate	Concentrations (mmol/L)	after mixing	30°C for 1 day	4°C for 1 day	4°C for 7 days
	Blank	7.77±0.01	7.76±0.01	7.77±0.01	7.77±0.01
	Ca 0 P 0	6.19±0.03	6.22±0.03	6.24±0.05	6.26±0.04
	Ca 0 P 50	5.69±0.02	5.79±0.14	5.80±0.12	5.82±0.12
Inorganic	Ca 20 P 20	6.13±0.02	6.09±0.07	6.12±0.09	6.14±0.09
	Ca 30 P 0	5.25±0.01	5.47±0.39	5.47±0.32	5.48±0.34
	Ca 30 P 50	5.80±0.02	5.98±0.15	6.04±0.09	5.11±0.05
	Ca 0 NaGP 0	6.71±0.01	6.72±0.02	6.74±0.02	6.74±0.04
	Ca 0 NaGP 50	6.62±0.01	6.65±0.05	6.67±0.04	6.68±0.02
NaGP	Ca 20 NaGP 20	6.80±0.02	6.83±0.02	6.85±0.03	6.87±0.03
	Ca 30 NaGP 0	6.33±0.02	6.35±0.02	6.36±0.02	6.38±0.01
	Ca 30 NaGP 50	6.89±0.04	6.91±0.04	6.91±0.02	6.95±0.03

Mean±SD,
Ca = Concentration of calcium gluconate (mmol/L), P = Concentration of dipotassium phosphate (mmol/L),
NaGP = Concentration of sodium glycerophosphate (mmol/L)

According to the absorbance of PN admixtures from spectrophotometer (table 3) and average particle size from Zetasizer Nano ZS (table 4), the results found that two sample formulas, containing calcium gluconate 30 mmol/L and inorganic phosphate 50 mmol/L and calcium gluconate 20 mmol/L and inorganic phosphate 20 mmol/L showed the precipitation during 7 days of analysis at any temperature.

Table 3. Absorbance of PN admixtures from spectrophotometer

Types of phosphate	Concentrations (mmol/L)	after mixing	30°C for 1 day	4°C for 1 day	4°C for 7 days
	Blank	0.000	0.000	0.000	0.000
	Ca 0 P 0	0.002±0.002	0.041±0.001	0.040±0.001	0.043±0.002
	Ca 0 P 50	0.001±0.001	0.042±0.001	0.039±0.001	0.042±0.001
Inorganic	Ca 20 P 20	0.910±0.110	0.779±0.002	0.837±0.002	0.839±0.001
	Ca 30 P 0	0.001±0.001	0.042±0.002	0.042±0.001	0.042±0.001
	Ca 30 P 50	1.014±0.205	1.031±0.002	1.094±0.002	1.097±0.002
	Ca 0 NaGP 0	0.047±0.001	0.042±0.001	0.041±0.001	0.043±0.002
	Ca 0 NaGP 50	0.042±0.002	0.040±0.001	0.041±0.002	0.042±0.001
NaGP	Ca 20 NaGP 20	0.044±0.001	0.041±0.001	0.039±0.001	0.040±0.001
	Ca 30 NaGP 0	0.041±0.001	0.040±0.001	0.038±0.001	0.041±0.001
	Ca 30 NaGP 50	0.042±0.001	0.039±0.001	0.039±0.001	0.039±0.001

Mean±SD,
Ca = Concentration of calcium gluconate (mmol/L), P = Concentration of dipotassium phosphate (mmol/L),
NaGP = Concentration of sodium glycerophosphate (mmol/L)

Table 4. Average particle size of PN admixtures (μm)

Types of phosphate	Concentrations (mmol/L)	after mixing	30°C for 1 day	4°C for 1 day	4°C for 7 days
	Blank	0.291±23.129	0.543±255.860	0.149±120.555	0.500±151.552
	Ca 0 P 0	0.348±216.031	0.126±17.753	0.134±70.579	0.067±21.112
	Ca 0 P 50	0.268±146.604	0.112±16.157	0.094±22.873	0.091±24.350
Inorganic	Ca 20 P 20	4.885±662.409	3.866±2261.200	4.049±668.518	3.552±1786.624
	Ca 30 P 0	0.372±361.215	0.290±201.388	0.326±95.634	0.342±101.137
	Ca 30 P 50	5.526±670.499	3.903±611.842	5.733±1618.815	5.319±1553.279
	Ca 0 NaGP 0	0.139±3.877	0.146±83.320	0.046±16.553	0.12f1±14.435
	Ca 0 NaGP 50	0.196±19.717	0.154±81.837	0.152±62.693	0.207±139.322
NaGP	Ca 20 NaGP 20	0.391±95.527	0.292±68.379	0.181±17.226	0.397±119.155
	Ca 30 NaGP 0	0.476±364.063	0.253±126.058	0.282±215.478	0.576±396.278
	Ca 30 NaGP 50	0.142±49.910	0.131±79.826	0.047±31.956	0.106±26.705

Mean±SD,
Ca = Concentration of calcium gluconate (mmol/L), P = Concentration of dipotassium phosphate (mmol/L),
NaGP = Concentration of sodium glycerophosphate (mmol/L)

Discussion

This preliminary result showed the compatibility of calcium and NaGP at the concentrations normally used in practice. All NaGP-containing formulas exhibited no precipitation along 7-day storage duration at both 4°C and 30°C while formulas containing high concentration of inorganic phosphate obviously showed precipitation. Inorganic phosphate; dipotassium phosphate, are easily dissociated and resulted in calcium monohydrogen phosphate precipitation. NaGP contains a phosphate group, which is covalently bonded to glycerol and no decomposition reaction; therefore, precipitation of calcium phosphate can be avoid even high concentration of mineral contents.[5, 8]

Conclusion

The compatibility of calcium and phosphate in parenteral solutions is seriously concerned in pediatrics due to high dosing of calcium and phosphorus at the saturation point. This study found that NaGP; a new source of phosphate, showed good compatibility with high concentration of calcium gluconate along 7-day storage duration at both 4°C and 30°C. However, further study was required to assess the safety, efficiency and cost-effectiveness of using sodium glycerophosphate in pediatric PN.

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