Calcium and Phosphate Solubility Curves for Parenteral Nutrient Solutions Containing Vaminolact®

LADDA MO-SUWAN, M.D.*,
AREERUK PUETPAIBOON, B.Sc. (Chemistry), M.Sc. (Biological Science)*,
BENJAMAPORN APIROMRAK, B.Sc. in Pharm**

Abstract

Calcium and phosphate incompatibility in the total parenteral nutrient (TPN) solutions is a common problem especially in neonates. Their combinations in TPN admixture must be tested before use. We here investigated the compatibility of calcium and phosphate in TPN solutions containing a newborn amino acid product, Vaminolact® . The TPN test-solutions contained 10 per cent dextrose, 1, 2, or 3 per cent Vaminolact® , 4 mmole/L of magnesium sulphate and various combinations of calcium gluconate and dipotassium phosphate. Precipitations and crystallizations were inspected visually and microscopically after 24 hours standing at room temperature. Solubility curves were made by plotting the maximum concentrations of calcium and phosphate at which both were still compatible in the solution. Such curves are extremely helpful for clinicians and pharmacists to administer maximum calcium and phosphate dose for individual patient requirement.

Compatibility of calcium and phosphate in the total parenteral nutrient solution (TPN) has been a concern. Two deaths and two injuries possibly related to a calcium phosphate precipitate were reported recently in the FDA safety alert(1). Autopsies revealed pulmonary emboli containing calcium phosphate. This fatal consequence can be prevented by strict adherence to the recommended protocol for intravenous admixture(2). To assure compatibility, it was recommended that combinations of calcium and phosphate in TPN fluids utilizing simulated worst-case scenarios must be tested before use(3). We previously reported the calcium and phosphate solubility curves for pediatric TPN solutions using three aminoacid products: Aminoplasmal-paed® , Aminovenos-N-pad® and Moripron-F® (4). In this report, we present such curves for TPN solution containing Vaminolact® , an aminoacid formulation specific for newborn and infants.

* Department of Pediatrics, Faculty of Medicine
** Pharmacy Department, Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand.

MATERIAL AND METHOD

As dextrose concentrations increase, *p*H of TPN solution decreases slightly and this may contribute to increased solubility of calcium-phosphate[5]. We then chose to do our experiment at the final dextrose concentration of 10 per cent, since the calcium-phosphate solubility in this concentration will be definitely soluble in the higher dextrose concentration. Moreover, the derived solubility curve will be beneficial to the wider range of users of parenteral nutrition. Concerning other ions, sodium, potassium, chloride, and acetate rarely cause solubility problems in TPN solutions[6], so they were not added in our solution samples. Magnesium effect on calcium-phosphate solubility is negligible[4,7], however, we chose to add magnesium at the fixed final concentration of 4 mmol/L to get the most appropriate curves.

The TPN samples were prepared containing fixed concentration of dextrose (as 50 per cent dextrose in water for injection) at 10 per cent and magnesium (as 50 per cent magnesium sulphate in water for injection, Atlantic Laboratories) at 4 mmol/L; and varying concentration of Vaminolact® (Pharmacia, Farmitalia Carlo Erba; composition of which is shown in Table 1), phosphate (as 8.7 per cent dipotassium phosphate, Otsuka Pharmaceuticals), and calcium (as 10 per cent calcium gluconate, Pharmaceutical Organization of Thailand). The sequence of mixing was as follows : sterile water, aminoacids, dextrose, phosphate, magnesium and calcium. The final volume was 10 ml. All samples were duplicated and prepared at room temperature inside the laminar air flow hood under sterile technique. They were mixed thoroughly during addition and at the end to eliminate local concentration of the additives. Final *p*H of each sample was measured by the Orion research digital *p*H/millivolt meter 611.

The experiments were performed at the aminoacid concentration of 1, 2 and 3 per cent. At each concentration, calcium and phosphate were both varied starting from 0.5 mmol/L, increasing by 0.5 mmol/L until precipitation occurred. After 24 hours standing at room temperature, the samples were visually inspected against a black background for evidence of precipitates. The clear samples were further checked under the microscope with polarizers at the power 40x for evidence of microcrystallization.

Table 1. Aminoacid composition of Vaminolact® .

	Content (g/100 g total aminoacid)*
L-Isoleucine	4.8
L-Leucine	10.8
L-Lysine	8.6
L-Methionine	2.0
L-Cysteine/cystine	1.5
L-Phenylalanine	4.2
L-Threonine	5.5
L-Tyrosine	0.8
L-Tryptophan	2.0
L-Valine	5.5
L-Alanine	9.7
L-Arginine	6.3
L-Aspartic acid	6.3
L-Glutamic acid	10.9
Glycine (amino acetic acid)	3.2
L-Histidine	3.2
L-Proline	8.6
L-Serine	5.8
Taurine	0.5

* Electrolyte-free solution

Solubility curves were made by plotting the maximum concentration of calcium and phosphate which were still compatible in the solution.

Titratable acidity of Vaminolact® was carried out as described by Sturgeon RJ et al[8] both in the undiluted solution and the one-to-one mixture of Vaminolact® with 50 per cent dextrose solution. The solution samples were adjusted to *p*H 5.0 with 2 N HCl, then titrated to *p*H 8.0 using 0.1001 N NaOH. The sodium hydroxide was delivered in 0.25 ml increments and the *p*H changes per addition were recorded. The titratable acidities (TA) were calculated using the following equation:

$$TA = (V_B - N_B \times 1000) / V_S$$

where V_B is the volume of sodium hydroxide added to the unadjusted solution (initial *p*H) to reach *p*H 7.4; N_B is the normality of sodium hydroxide (in meq/ml); and V_S is the volume (in ml) of the sample titrated.

RESULT

Fig. 1 demonstrates the calcium-phosphate solubility curves for TPN solutions containing Vaminolact® . All points to the right of each curve represent concentrations of calcium and phosphate at which precipitation occurred. Maximum com-

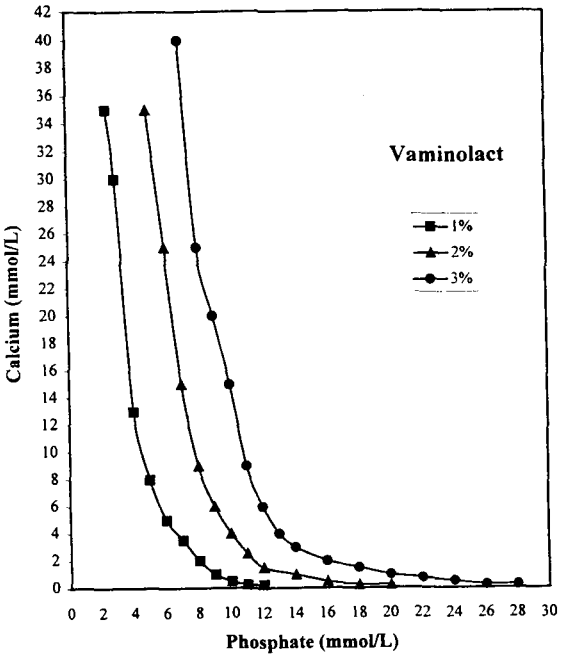

Fig. 1. Calcium and phosphate solubility curves for parenteral nutrient solutions containing 10 per cent dextrose, 1-3 per cent Vaminolact® , 4 mmol/L magnesium sulphate. All points to the right of the curve result in precipitation.

Table 2. Maximum compatible concentration of calcium and phosphate and final *p*H of TPN samples.

Concentration of Vaminolact® in TPN sample* (g/dL)	Final *p*H	Maximum Ca/P concentration** (mmoL/L)
1	6.43	5.5
2	6.27	8.0
3	6.20	10.5

* Containing 10 per cent dextrose, 4 mmol/L MgSO4.
** At the calcium to phosphate molar ratio of 1:1.

Table 3. Titratable acidities of Vaminolact® .

Vaminolact®		Initial *p*H	Titratable acidity*
6.35	per cent aminoacid solution	5.15	21.02
3.27	per cent aminoacid solution + 25 per cent dextrose**	5.00	11.71

* Used 0.1001 N NaOH.
** One-to-one mixture of Vaminolact® with 50 per cent dextrose.

patible calcium-phosphate concentration (at the molar ratio of 1:1) in the TPN samples at different levels of Vaminolact® and titratable acidities of the product are shown in Table 2 and 3 respectively.

DISCUSSION

Combination of calcium and phosphate in a single solution can result in precipitation. This well-known phenomenon is a frequent problem in the admixture of neonatal nutrient solutions in which high contents of both minerals are required for growth in this age group. We here present the solubility curves of calcium and phosphate in the parenteral nutrient solutions using Vaminolact® as the aminoacid source. To our knowledge, there have been no such curves before.

In order to prevent precipitation, Greene et al[3] has recommended mixing calcium and phosphate at the ratio of 1.3:1 by weight or 1:1 by molar ratio. The recommended neonatal TPN admixture is 50-60 mg/dl calcium and 40-45 mg/dl phosphate with 25 g aminoacid/L and fluid uptake of 120-150 ml/kg. Practically the individual patient's requirement of calcium and phosphate frequently does not fit the recommended ratio. The curves presented here and previously[4], which were based on the products available in Thailand, will allow physicians and pharmacists how to administer both minerals to meet the particular group of patients without harmful complications.

Factors affecting solubility of calcium and phosphate in the TPN admixtures include *p*H of the solution, dextrose concentration, concentration and composition of the aminoacid solutions, salt forms of calcium, the sequence in which calcium and phosphate are added, temperature and standing time [3-4,9-12]. Being less dissociable, it was found that calcium gluconate, the salt form used in the present study, permitted a higher amount of phosphate to be added than the calcium chloride did[9].

Formulation and concentration of aminoacids could both affect calcium and phosphate solubility. Similar to other studies[4,10-12], the higher the concentration of aminoacids, the greater the amount of calcium and phosphate could be added as shown in Fig. 1 and Table 2. Different aminoacid formulations provide different buffer capacities[4,8,12]. From our previous study[4], comparing three aminoacid products, calcium-phosphate solubility is highest in the solution containing Moripron-F® (maximum concentration = 5.5, 8.0, 10.5 mmol/L at the aminoacid levels of 1, 2 and 3 g/dl respectively). With similar attainment of maximum calcium-phosphate concentration, Vaminolact® offers advantage over Moripron-F® regarding the development of metabolic acidosis which is a concern in administration of TPN in newborn and infants. Having lower titratable acidity, Vaminolact® presents less hydrogen ion load to the patients than Moripron-F® did (titratable acidities of 10% Moripron F® and 5% Moripron-F® plus 25% dextrose = 49.6 and 53.4 mEq/L respectively[4]). This may not be a problem and of less concern in older patients.

Importance of quality assurance in compounding TPN solution when calcium and phosphate are mixed in the same solution has been re-emphasized[2] after the safety alert report of the FDA[1]. Warmth, favoring calcium phosphate precipitates[10-12], of room and body temperature was suggested to be one of the causes of fatality[13]. Parenteral nutrient solutions inspected only when they are just taken out of the refrigerated storage in the pharmacy room form precipitates in a warmer room or body temperature. The present curves and our previous ones[4] derived from leaving the tested samples 24 hours at room temperature (maximum) can assure their users of safety from such problems to some extent.

SUMMARY

Calcium phosphate precipitation when both ions are mixed in the same TPN solution is a concern in neonates. Their combinations in TPN admixtures using the worst-case scenarios must be tested before use. We here investigated the compatibility of calcium and phosphate in TPN samples utilizing the newborn aminoacid product, Vaminolact® . The test-samples contained 10 per cent dextrose, 4 mmol/L magnesium sulphate, 1-3 per cent Vaminolact® and various combinations of calcium gluconate and dipotassium phosphate. Precipitates and crystallization were inspected visually and microscopically after 24 hours standing at room temperature. Calcium-phosphate solubility curve were drawn. Such curves will enable the clinicians and pharmacists to provide maximum calcium and phosphate in TPN solution as needed without subsequent precipitation.

(Received for publication on July 26, 1996)

REFERENCES

1. Food and Drug Administration. Safety alert : hazards of precipitation associated with parenteral nutrition. Am J Hosp Pharm 1994; 51: 1427-8.
2. Trissel L A. Compounding our problems. Am J Hosp Pharm 1994; 51: 1534.
3. Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition : report of the subcommittee on pediatric parenteral nutrient requirements from the committee on clinical practice issues of The American Society for Clinical Nutrition, Am J Clin Nutr 1988; 48: 1324-42.
4. Mo-suwan L, Apiromrak B, Puetpaiboon A. Calcium and Phosphate Solubility Curves for Parenteral Nutrient Solutions containing Aminoplasmal-paed®, Aminovenos-N-pad® or Moripron-F®. J Med Assoc Thai 1993; 76: 688-92.
5. Poole RL. Problems with preparation of parenteral nutrition solutions. In: Kerner JA, ed. Manual of pediatric parenteral nutriton. New York: John Wiley & Sons, Inc; 1983: 185.
6. Giovanoni R. The manufacturing of pharmacy solutions and incompatibilities. In: Fisher JE, ed. Total parenteral nutrition. Boston: Little, Brown and Company; 1976: 27.
7. Boulet M, Marrier JR, Rose D. Effect of magnesium on formation of calcium phosphate precipitates. Arch Biochem Biophys 1962; 96: 629-36.
8. Sturgeon RJ, Athanikar NK, Henry RS, et al. Titratable acidities of crystalline amino acid admixtures. Am J Hosp Pharm 1980; 37: 388-90.
9. Henry RS, Jurgens RW, Sturgeon R, et al. Compatibility of calcium chloride and calcium gluconate with sodium phosphate in a mixed TPN solution. Am J Hosp Pharm 1980; 37: 673-4.
10. Eggert LD, Rusho WJ, Mackay MW, Chan GM. Calcium and phosphorus compatibility in parenteral nutrition solutions for neonates. Am J Hosp Pharm 1982; 39: 49-53.
11. Fitzgerald KA, Mackay MW. Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing TrophAmine. Am J Hosp Pharm 1986; 43: 88-93.
12. Lenz GT, Mikrut BA. Calcium and phosphate solubility in neonatal parenteral nutrient solutions containing Aminosyn PF or TrophAmine. Am J Hosp Pharm 1988; 45: 2367-71.
13. Hasegawa GR. Caring about stability and compatibility. Am J Hosp Pharm 1994; 51: 1533-4.

การละลายของแคลเซียมและฟอสเฟต ในสารละลายอาหารที่มีวามิโนแลคท์®

ลัดดา เหมาะสุวรรณ, พ.บ.,*

อารีรักษ์ พีชน์ไพบูลย์, วท.บ. (เคมี), วท.ม. (วิทยาศาสตร์ชีวภาพ),*

*เบญจมาภรณ์ อภิรมย์รักษ์, ภ.บ.***

การตกตะกอนของแคลเซียมและฟอสเฟตเมื่อผสมด้วยกันในสารละลายอาหารที่ให้ทางหลอดเลือดดำเป็นปัญหาที่พบบ่อยในสารละลายที่ให้ทารก ผู้ใช้จึงควรที่จะศึกษาทดลองการละลายก่อนที่จะนำไปใช้ในเวชปฏิบัติ คณะผู้วิจัยได้ทำการศึกษาการละลายของแร่ธาตุทั้งสองนี้ในสารละลายอาหารที่ให้ทางหลอดเลือดดำ ที่ใช้สารละลายกรดอะมิโน Vamimolact® วิธีการศึกษา : ผสมเด็กซโตรส 10%, Vaminolact 1, 2 หรือ 3%, แมกนีเซียมฟอสเฟต 4 มิลลิโมลต่อลิตร และแคลเซียมกับฟอสเฟตที่ความเข้มข้นต่าง ๆ กัน ตั้งไว้ที่อุณหภูมิห้องนาน 24 ชั่วโมง แล้วนำมาตรวจหาตะกอนหรือผลึกด้วยตาเปล่า และกล้องจุลทรรศน์ นำค่าสูงสุดที่ยังละลายได้ของแคลเซียมและฟอสเฟตที่ความเข้มข้นต่าง ๆ กันมาสร้างเป็นกราฟ กราฟนี้มีประโยชน์มากสำหรับแพทย์และเภสัชกร ในการสั่งผสมแคลเซียมและฟอสเฟตสำหรับการให้อาหารทางหลอดเลือดดำได้สูงตรงตามความต้องการของผู้ป่วย

* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยสงขลานครินทร์,

** แผนกเภสัชกรรม, โรงพยาบาลสงขลานครินทร์, อ. หาดใหญ่, จ. สงขลา 90112