

Calcium and phosphate solubility curves for parenteral  
nutrient solutions containing Vaminolact<sup>®</sup>



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Title Page

**Title** Calcium and phosphate solubility curves for parenteral nutrient solutions containing Vaminolact<sup>R</sup>

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**Short running title** : Calcium and phosphate solubility in TPN solutions

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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 was reported recently in the FDA safety alert<sup>(1)</sup>. Autopsies revealed pulmonary emboli containing calcium phosphate. This fatal consequence can be prevented by strict adherence to the recommended protocol for intravenous admixture<sup>(2)</sup>. 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<sup>(3)</sup>. We previously reported the calcium and phosphate solubility curves for pediatric TPN solutions using three aminoacid products: Aminoplasmal-paed<sup>R</sup>, Aminovenos-N-pad<sup>R</sup> and Moripron-F<sup>R</sup><sup>(4)</sup>. In this report, we present such curves for TPN solution containing Vaminolact<sup>R</sup>, an aminoacid formulation specific for newborn and infants.

## Materials and methods

As dextrose concentrations increase, pH of TPN solution decreases slightly and this may contribute to increased solubility of calcium-phosphate<sup>(5)</sup>. We then chose to do our experiment at the final dextrose concentration of 10 percent, 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<sup>(6)</sup>, so they were not added in our solution samples. Magnesium effect on calcium-phosphate solubility is negligible<sup>(4,7)</sup>, 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 percent dextrose in water for injection) at



10 percent and magnesium (as 50 percent magnesium sulphate in water for injection, Atlantic Laboratories) at 4 mmol/L; and varying concentration of Vaminolact<sup>®</sup> (Pharmacia, Farmitalia Carlo Erba; composition of which is shown in the Table 1), phosphate (as 8.7 percent dipotassium phosphate, Otsuka Pharmaceuticals), and calcium (as 10 percent calcium gluconate, Pharmaceutical Organization of Thailand). The sequence of mixing was as follow : 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 pH of each sample was measured by the Orion research digital pH/millivolt meter 611.

The experiments were performed at the aminoacid concentration of 1, 2 and 3 percent. 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 further checked under the microscope with polarizers at the power 40x for evidence of microcrystallization.

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

Titratable acidity of Vaminolact<sup>®</sup> was carried out as described by Sturgeon RJ et al<sup>(8)</sup> both in the undiluted solution and the one-to-one mixture of Vaminolact<sup>®</sup> with 50% dextrose solution. The solution samples were adjusted to pH 5.0 with 2 N HCl, then titrated to pH 8.0 using 0.1001 N NaOH. The sodium hydroxide was delivered in 0.25 ml increments and the pH 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 pH) to reach pH 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.

## Results

Figure 1 demonstrates the calcium-phosphate solubility curves for TPN solutions containing Vaminolact<sup>R</sup>. All points to the right of each curve represent concentrations of calcium and phosphate at which precipitation occurred. Maximum compatible calcium-phosphate concentration (at the molar ratio of 1:1) in the TPN samples at different levels of Vaminolact<sup>R</sup> and titratable acidities of the product are shown in the 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<sup>R</sup> as the aminoacid source. To our knowledge, there are no such curves before.

In order to prevent precipitation, Greene et al<sup>(3)</sup> 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<sup>(4)</sup>, which were based on the products available in Thailand, will allow physicians and pharmacists 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 pH 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<sup>(3-4,9-12)</sup>. Being less dissociable, it was found that calcium gluconate, the salt form used in the present study, permitted higher amount of phosphate to be added than the calcium chloride did<sup>(9)</sup>.

Formulation and concentration of aminoacids could both affect calcium and phosphate solubility. Similar to other studies<sup>(4,10-12)</sup>, the higher the concentration of aminoacids, the greater the amount of calcium and phosphate could be added as shown in the Fig 1 and the Table 2. Different aminoacid formulations provide different buffer capacities<sup>(4,8,12)</sup>. From our previous study<sup>(4)</sup>, comparing three aminoacid products, calcium-phosphate solubility is highest in the solution containing Moripron-F<sup>R</sup> (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<sup>R</sup> offers advantage over Moripron-F<sup>R</sup> regarding the development of metabolic acidosis which is a concern in administration of TPN in newborn and infants. Having lower titratable acidity, Vaminolact<sup>R</sup> presents less hydrogen ion load to the patients than Moripron-F<sup>R</sup> did (titratable acidities of 10% Moripron F<sup>R</sup> and 5% Moripron-F<sup>R</sup> plus 25% dextrose = 49.6 and 53.4 mEq/L respectively<sup>(4)</sup>). This may not be a problem and 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<sup>(2)</sup> after the safety alert report of the FDA<sup>(1)</sup>. Warmth, favoring calcium phosphate precipitates<sup>(10-12)</sup>, of room and body temperature was suggested to be one of the cause of fatality<sup>(13)</sup>. 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<sup>(4)</sup> derived from leaving the tested samples 24 hours at room temperature (maximum) can assure their users of safety from such problem 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<sup>R</sup>. The test-samples contained 10 percent dextrose, 4 mmol/L magnesium sulphate, 1-3 percent Vaminolact<sup>R</sup> 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.



Table 1 Aminoacid Composition of Vaminolact<sup>R</sup>

Content (g/100 g total aminoacid) <sup>1</sup>	
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

<sup>1</sup>Electrolyte-free solution



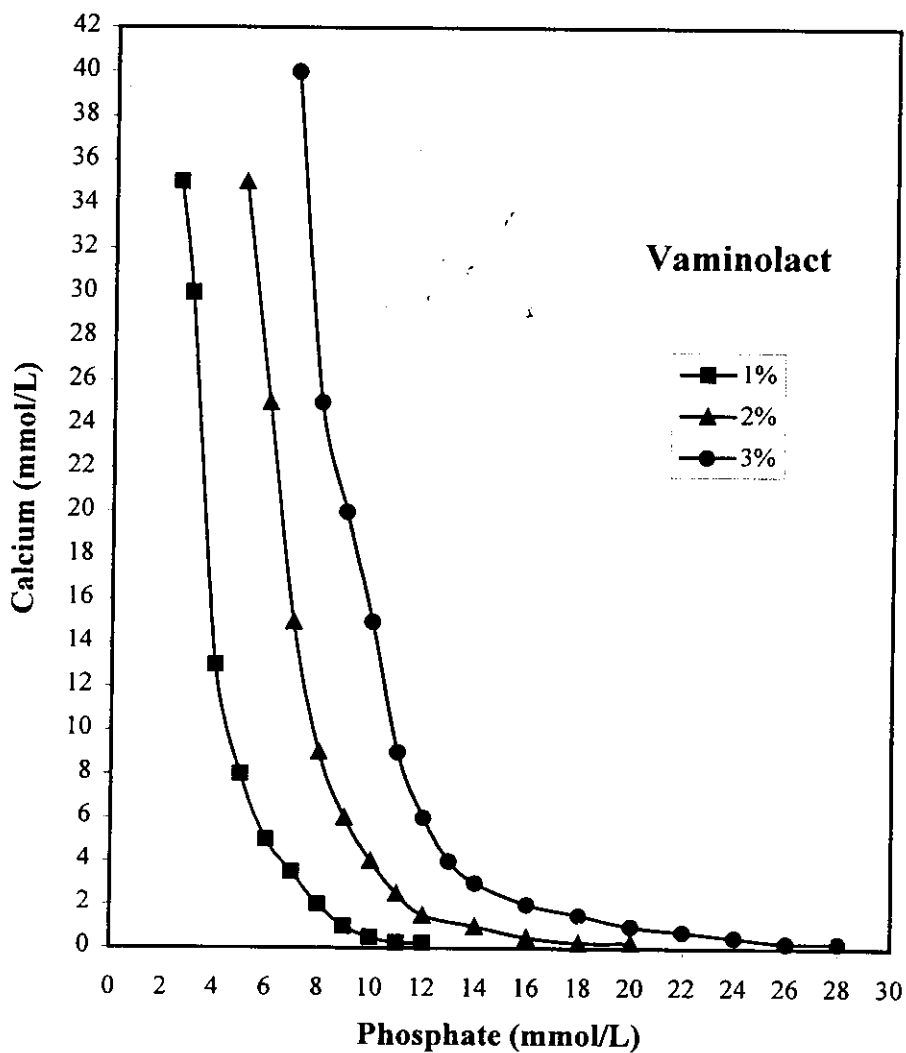


Fig.1 Calcium and phosphate solubility curves for parenteral nutrient solutions containing 10 percent dextrose, 1-3 percent Vaminolact<sup>®</sup>, 4 mmol/L magnesium sulphate. All points to the right of the curve result in precipitation.



Table 2 Maximum compatible concentration of calcium and phosphate  
and final pH of TPN samples

Concentration of Vaminolact <sup>R</sup> in TPN sample <sup>1</sup> (g/dL)	Final pH	Maximum Ca/P concentration <sup>2</sup> (mmol/L)
1	6.43	5.5
2	6.27	8.0
3	6.20	10.5

<sup>1</sup>Containing 10 percent dextrose, 4 mmol/L MgSO<sub>4</sub>.

<sup>2</sup>At the calcium to phosphate molar ratio of 1:1.

Table 3 Titratable acidities of Vaminolact<sup>R</sup>

Vaminolact <sup>R</sup>	Initial pH	Titratable acidity <sup>1</sup>
6.35 per cent aminoacid solution	5.15	21.02
3.27 per cent aminoacid solution + 25 percent dextrose <sup>2</sup>	5.00	11.71

1. Used 0.1001 N NaOH.

2. One-to-one mixture of Vaminolact<sup>R</sup> with 50 per cent dextrose.



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nutrient solutions containing Vaminolact<sup>R</sup>

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การตกตะกอนของแคลเซียมและฟอสเฟตเมื่อผสมด้วยกันในสารละลายอาหารที่ให้ทาง  
หลอดเลือดดำเป็นปัญหาที่พบบ่อยในสารละลายที่ให้ทารก ผู้ใช้จึงควรที่จะศึกษาทดลองการ  
ละลายก่อนที่จะนำไปใช้ในเวชปฏิบัติ คณะผู้วิจัยได้ทำการศึกษาการละลายของแร่ธาตุทั้งสอง  
นี้ในสารละลายอาหารที่ให้ทางหลอดเลือดดำ ที่ใช้สารละลายกรดอะมิโน Vaminolact<sup>R</sup>

วิธีการศึกษา : ผสมเด็กซ์โตรส 10%, Vaminolact 1, 2 หรือ 3%, แมกนีเซียมฟอสเฟต  
4 มิลลิโมลต่อลิตร และแคลเซียมกับฟอสเฟตที่ความเข้มข้นต่าง ๆ กัน ตั้งไว้ที่อุณหภูมิห้องนาน  
24 ชั่วโมง แล้วนำมาตรวจหาตะกอนหรือผลึกด้วยตาเปล่า และกล้องจุลทรรศน์ นำค่าสูงสุด  
ที่ยังละลายได้ของแคลเซียมและฟอสเฟตที่ความเข้มข้นต่าง ๆ กันมาสร้างเป็นกราฟ  
กราฟนี้มีประโยชน์มากสำหรับแพทย์และเภสัชกร ในการสั่งผสมแคลเซียมและฟอสเฟตสำหรับ  
การให้อาหารทางหลอดเลือดดำได้ถูกต้องตรงตามความต้องการของผู้ป่วย (เมทสาร. ส่วนต้นฉบับ)

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