Nutrición Hospitalaria

Nutrición Hospitalaria
ISSN: 0212-1611
ISSN: 1699-5198
Grupo Arán

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The presence of inorganic calcium in pediatric parenteral admixtures
Nutrición Hospitalaria, vol. 35, no. 1, 2018, January-February, pp. 11-18
Grupo Arán

DOI: https://doi.org/10.20960/nh.1340

Available in: https://www.redalyc.org/articulo.oa?id=309258226004

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ISSN (electrónico): 1699-5198 - ISSN (papel): 0212-1611 - CODEN NUHOEQ S.V.R. 318

ARÁN

Nutrición Hospitalaria

Trabajo Original

Nutrición artificial

The presence of inorganic calcium in pediatric parenteral admixtures

Presencia de calcio inorgánico en las soluciones pediátricas de nutrición parenteral

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Abstract

Introduction: Newborn infants and small children require large amounts of calcium and phosphate in a low volume of solution which can increase the risk of precipitation of calcium phosphate. Calcium gluconate is the predominant calcium salt form employed in parenteral nutrition (PN) compounding due to its solubility profile with phosphate. Unfortunately, calcium gluconate contains higher levels of aluminum contamination than calcium chloride, resulting in an increased potential for aluminum toxicity in patients receiving traditional PN. The physicochemical stability of 30 total parenteral admixtures containing inorganic calcium salts was evaluated.

Methods: Parenteral admixtures were prepared in one-chamber ethylene vinyl acetate bags: amino acids, glucose, electrolytes including only inorganic calcium salt and 20% (w/w) lipid emulsions (SMOFlipid®, Omegaven® or Lipofundin MCT/LCT®) were placed together in a one chamber bag. Admixtures were stored at +4 °C for up to eight days after preparation. Visual observations, globule size distribution (using optical microscopy, laser diffraction and photon correlation spectroscopy methods), pH analysis and zeta potential measurements were performed.

Results: The physicochemical stability of 29 of parenteral admixtures in the presence of inorganic calcium salt was confirmed. One admixture was deemed unsuitable for use in clinical practice due to the coalescence of oil droplets.

Conclusion: Despite the presence of inorganic calcium salts, pediatric parenteral admixtures were stable up to eight days of storage. Due to presence of multiple components and a high risk of incompatibilities, physicochemical studies should be performed for each admixture before use in clinical practice.

Key words:

Pediatric parenteral nutrition. Physicochemical stability. Parenteral emulsion. Inorganic calcium. Home parenteral nutrition.

Resumen

Introducción: los recién nacidos y los lactantes precisan aportes elevados de calcio y fósforo en soluciones con pequeño volumen lo que aumenta el riesgo de formar precipitados de fosfato cálcico. La principal sal de calcio empleado en nutrición parenteral (NP) es el gluconato cálcico, debido a su perfil de solubilidad con el fosfato. Lamentablemente el gluconato cálcico contiene unas concentraciones elevadas de aluminio mayores que el cloruro cálcico, lo que resulta en riesgo potencial de toxicidad por aluminio en pacientes que reciben NP. En este trabajo se evalúa la estabilidad fisicoquímica de 30 mezclas de NP con sales de calcio inorgánico.

Métodos: las mezclas de NP se prepararon en bolsas de acetato de etilenvinilo. En una bolsa unicameral se mezclaron aminoácidos, glucosa, y electrolitos incluyendo una sal de calcio inorgánico y una emulsión lipídica al 20% (SMOFlipid®, Omegaven® o Lipofundin MCT/LCT®). Las mezclas se almacenaron a +4 ° C hasta 8 días tras la elaboración. Se realizó un examen visual, estudio de la distribución del tamaño de los glóbulos (mediante microscopía óptica, difracción por láser y espectroscopia fotónica), análisis de pH y medición del potencial zeta.

Resultados: se confirmó la estabilidad fisicoquímica de 29 mezclas de NP que contenían sales de calcio inorgánico. Sólo una de las preparaciones se consideró inválida para su uso clínico debido a la coalescencia de las gotas de grasa.

Conclusión: a pesar de la presencia de sales de calcio inorgánico, las mezclas de NP pediátrica fueron estables hasta 8 días de almacenamiento. La presencia de múltiples componentes y el riesgo elevados de incompatibilidades hace recomendable el estudio de estabilidad fisicoquímica de cada mezcla antes de su empleo en la clínica.

Palabras clave:

Nutrición parenteral pediátrica. Estabilidad fisicoquímica. Emulsión. Calcio inorgánico. Nutrición parenteral pediátrica.

Received: 07/06/2017 • Accepted: 27/09/2017

Acknowledgements: The authors wish to thank Hospital Pharmacy of The Children's Memorial Health Institute of Warsaw, Poland, for preparing the TPN admixtures and Fresenius Kabi for providing their products for the study.

Watrobska-Swietlikowska D, MacLoughlin R, Szlagatys-Sidorkiewicz A. The presence of inorganic calcium in pediatric parenteral admixtures. Nutr Hosp 2018;35:11-18

DOI: http://dx.doi.org/10.20960/nh.1340

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INTRODUCTION

Management of intestinal failure requires parenteral nutrition. For patients dependent on parenteral nutrition for longer than three months, home parenteral nutrition (HPN) is an opportunity for shortened hospital stays. The main indications for HPN in children include digestive tract diseases such as short bowel syndrome (59%), congenital enteropathies (10%), chronic pseudo-obstruction syndrome (9%) and inflammatory bowel diseases (5%) (1). In the vast majority of children, intestinal failure begins during the neonatal period and usually persists throughout the first years of life. The main aim of the complex treatment of children with intestinal failure is to achieve optimal growth and weight gain, and so the provision of macro- and micronutrients is crucial. The high energy and protein demand of dynamically growing and developing pediatric patients together with the possible loss of nutrients due to diarrhea, impaired motility or high stoma output, presents a significant challenge in preparing nutritional admixtures. In the early stages after surgical resection, anti-secretory drugs are useful to decrease both stoma output and stool volume (2). Total parenteral nutrition (PN) admixtures may be composed of different compounds which are mixed together, and so compatibility and stability must be considered (3). This is especially true for parenteral admixtures administered to premature infants, given the low final dose volume (4). The most critical parameters are the physical stability of these admixtures and the droplet size of the emulsions. If the droplet size exceeds the size of erythrocytes (6-8 μm), embolism can occur, which may have fatal consequences. The droplet size is influenced by many factors such as: the presence of electrolytes, especially those with a positive charge, can change the negative charge of the droplet surface of lipid emulsion (zeta potential), resulting in the coalescence of the droplets and even phase separation (5). All components, including vitamins, should mix together in order to avoid the requirement for patient manipulation in total parenteral nutrition (TPN) admixtures (6), and secondly, the presence of vitamins in PN protects lipid emulsions from oxidation (7). The second concern is the possibility of precipitation of calcium phosphate in pediatric parenteral admixtures. The most daunting problem for pharmaceutical preparation practices of PN is related to the day-to-day change of volume and formulation nutrients, due to changing clinical conditions and maturation. Considering the low dose volumes used in neonatology (as low as 1-2 ml), it is vital to ensure both physicochemical compatibility and adequate calcium and phosphorus supply (8). Further, newborn infants and small children require large amounts of calcium and phosphate in these low dose volumes which may increase the risk of precipitation of calcium phosphate (9,10). Precipitation can cause respiratory distress and pulmonary embolism (11). Inorganic phosphate in PN has the potential of forming precipitates with calcium, especially when using calcium chloride. As such, calcium gluconate is the predominant calcium salt form employed in PN compounding due to its solubility profile with phosphate. Unfortunately, calcium gluconate contains higher levels of aluminum contamination than calcium chloride, resulting in an increased potential for aluminum toxicity in patients receiving traditional PN. The risk of aluminum toxicity is especially present in the neonatal population, in whom higher per kilogram of bodyweight amounts of calcium and phosphates are administered. Organic sodium glycerophosphate (NaGP), with the divalent calcium ion, has a lower propensity towards precipitation than inorganic phosphate, thereby allowing for calcium chloride utilization. Data presented in this study demonstrating NaGP and calcium chloride compatibility provide a clinical option for limiting aluminum contamination while providing sufficient calcium and phosphate to meet the needs of neonatal patients. Although NaGP is approved for use in Europe, it lacks full American Food and Drug Administration approval except on a temporary basis during phosphate drug shortages.

The aim of the study was to determine the physicochemical stability of admixtures for PN, prepared in one-chamber bags, designed for pediatric patients who receive PN at home. The stability of 30 compositions of admixtures up to eight days of storage at +4 °C was evaluated. The admixtures characterized contained increasing amount of electrolytes, and the consequent value of CAN (critical aggregation number) parameter ranged from 300 to 1402. The admixtures were prepared in the one-chamber bags Exacta-Mix Eva (ethylene vinyl acetate) Bag Parenteral (Baxa Ltd., United Kingdom) at the Hospital Pharmacy. Vitamins were added just before analysis. Three types of lipid emulsions: SMOFlipid, Lipofundin MTC/LCT or Omegaven were used. All admixtures were composed only of inorganic calcium salt. The composition of the parenteral admixtures under test was designed by clinicians from the Children's Memorial Health Center Institute in Warsaw, Poland.

METHODS

COMPOUNDING OF ADMIXTURES FOR PARENTERAL NUTRITION IN HOSPITAL PHARMACY

Incomplete (without vitamins) TPN admixtures were prepared in the Pharmacy of the Children's Memorial Health Center in Warsaw, Poland, in compliance with pharmaceutical standards. Single-chamber bags, Exacta-Mix Eva Bag Parenteral, constituting the packaging of mixtures of the TPN were filled in a laminar flow system with sterile, air, purity class A. For this purpose, a Baxa 24 computer-controlled mixer was used, allowing for precise transfusion following base fluids, i.e., 40% dextrose solution (B. Braun Melsungen, Germany), amino acid solution (Aminoven® Infant 10%, Fresenius Kabi, Uppsala, Sweden or Vamin® 18 EF), water for injections, the lipid emulsion (Lipofundin® MCT/LCT, B. Braun Melsungen, Germany, Omegaven® or Smoflipid®, Fresenius Kabi, Austria), and preparation of organic phosphate (Glycophos®), sodium chloride (Natrium chloratum 10%, Polpharma, Starogard Gdanski, Poland), potassium chloride solution (Kalium chloratum 15%, WZF Polfa, Warsaw, Poland), magnesium sulphate solution (Magnesii sulfuricum 20%, Polpharma, Starogard Gdanski, Poland) and calcium chloride solution (Calcii chloratum 10%), trace elements (Addamel® or Peditrace®, Fresenius Kabi, Uppsala, Sweden).

TPN mixtures were protected from light. Following preparation, the mixtures were sent on the same day to Gdansk, where physicochemical analysis was performed. Vitamins (Soluvit® N dissolved in Vitalipid® N Infant, Fresenius Kabi, Uppsala, Sweden, or Cernevit®, Fresenius Kabi, Uppsala, Sweden) were added at the Department of Pharmaceutical Technology of GUMed injecting into the bag with the mixture just before each analysis. In Poland, and differently than other places in Europe, patients themselves add vitamins to PN admixtures prior to administration. The composition of the TPN admixtures are provided in table I.

STORAGE OF INCOMPLETE AND COMPLETE ADMIXTURES TPN

Parenteral admixtures were stored for up to eight days at refrigerated temperature (4 °C). Prior to analysis, mixtures were removed from the refrigerator, and stored for two hours at room temperature (21 ± 1 °C), the vitamins were added (t = 8 days) (Table I). After sampling, the mixtures were stored up to 24 hours at room temperature (21 ± 1 °C) in the dark, then analyzed (t = 8 days + 24h) (Fig. 1).

ADDITION OF VITAMINS

Parenteral admixtures were completed through the addition of vitamins (Table I). Vitamins were added under non-aseptic conditions, to better mimic the expected conditions of this stage, e.g. if a patient is at home. Vitamins were prepared by dissolving the freeze-dried water-soluble vitamins (Soluvit® N) in the fat emulsion comprising a vitamin soluble in the oil phase (Vitalipid® N) or Cernevit® in 0.9% sodium chloride injection (a mixture number: 25, 27, 30). For this purpose, each vial of Soluvit® N was added to 10 ml of Vitalipid® Infant and stirred to dissolve the Cernevit® vial in 10 ml of 0.9% sodium chloride solution for injection, and stirred until dissolved. Thus, dissolved vitamins were added using a syringe with a needle with filter in a prescribed amount to the TPN admixture.

Table I. Concentration of electrolytes (mmol/l), CAN and CaxP parameters of TPN admixtures

TPN	Na^+	K^+	Ca^{2+}	Mg^{2+}	CaxP	CAN
1	30.2	62.5	7.3	6.9	43.0	1000
2	26.3	15.4	6.6	2.6	43.4	632
3	14.6	16.6	5.1	3.6	7.7	589
4	18.1	13.8	5.6	5.5	21.7	747
5	20.6	32.6	5.9	1.8	35.3	545
6	66.0	27.3	4.9	4.4	14.0	690
7	47.3	22.7	4.3	4.5	32.0	633
8	15.9	13.1	7.9	1.8	26.0	647
9	22.7	34.5	4.7	4.1	4.7	616
10	39.9	18.9	9.1	10.8	24.7	1336
11	29.2	30.7	6.0	5.9	40.0	820
12	55.6	35.6	5.5	3.6	15.3	670
13	28.4	18.0	6.3	0.8	25.2	501
14	24.8	7.0	3.1	1.4	11.0	322
15	25.0	22.5	6.0	1.8	40.3	544
16	45.4	44.7	7.7	4.1	40.0	850
17	17.1	59.3	9.4	1.9	3.8	799
18	28.7	27.2	5.5	3.9	33.2	655
19	29.8	10.5	4.2	2.5	17.8	473
20	76.5	42.8	8.1	9.2	26.8	1229
21	10.9	46.3	4.6	6.0	25.1	735
22	37.7	39.9	7.5	3.5	0	783
23	28.5	14.5	3.3	0.7	8.8	297
24	30.3	35.3	8.3	5.1	46.7	926
25	54.3	58.4	6.0	9.0	6.0	1073
26	22.6	50.4	8.1	9.3	33.0	1189
27	11.3	14.9	6.9	8.3	17.3	1001
28	44.6	30.5	7.4	2.8	17.6	728
29	25.2	45.7	4.4	4.9	2.1	667
30	13.4	40.8	10.2	10.9	9.2	1402

PHYSICOCHEMICAL ANALYSIS OF COMPLETE PARENTERAL ADMIXTURES

The design of the physicochemical stability test is presented in figure 1. Analysis of the complete admixtures was carried out immediately after transportation (t = 24h) and after 24 hours of storage at room temperature, with light protection (t = 24h + 24h). Activation of pre-admixtures was at t = 24h or after eight days of storage. Completed parenteral admixtures were subjected to physicochemical stability analyses consisting of visual inspection, microscopic observation (biologic microscope with camera B1 223A Motic, Wetzlar, Germany), determination of oily globules size distribution - laser diffractometer (MasterSizer E Malvern Instruments, Malvern, UK) and photon correlation spectroscopy (Zetasizer, Malvern Instruments, Malvern, UK), zeta potential (Zetasizer, Malvern Instruments, Malvern, UK), pH measurement (pH meter Orion 350, Beverly, USA, with combination electrode). Before each pH measurement, a two point calibration of the pH meter was done, each with a buffer solution of pH 9.00 and pH 4.00, respectively. The pH 7.00 solution was used afterwards as a control. Between the calibration steps, the electrode was rinsed with distilled water and wiped dry. Each sample was measured after five minutes of equilibration.

The physical stability of parenteral admixtures was assessed by lipid droplet measuring in a light microscope with an upper droplet

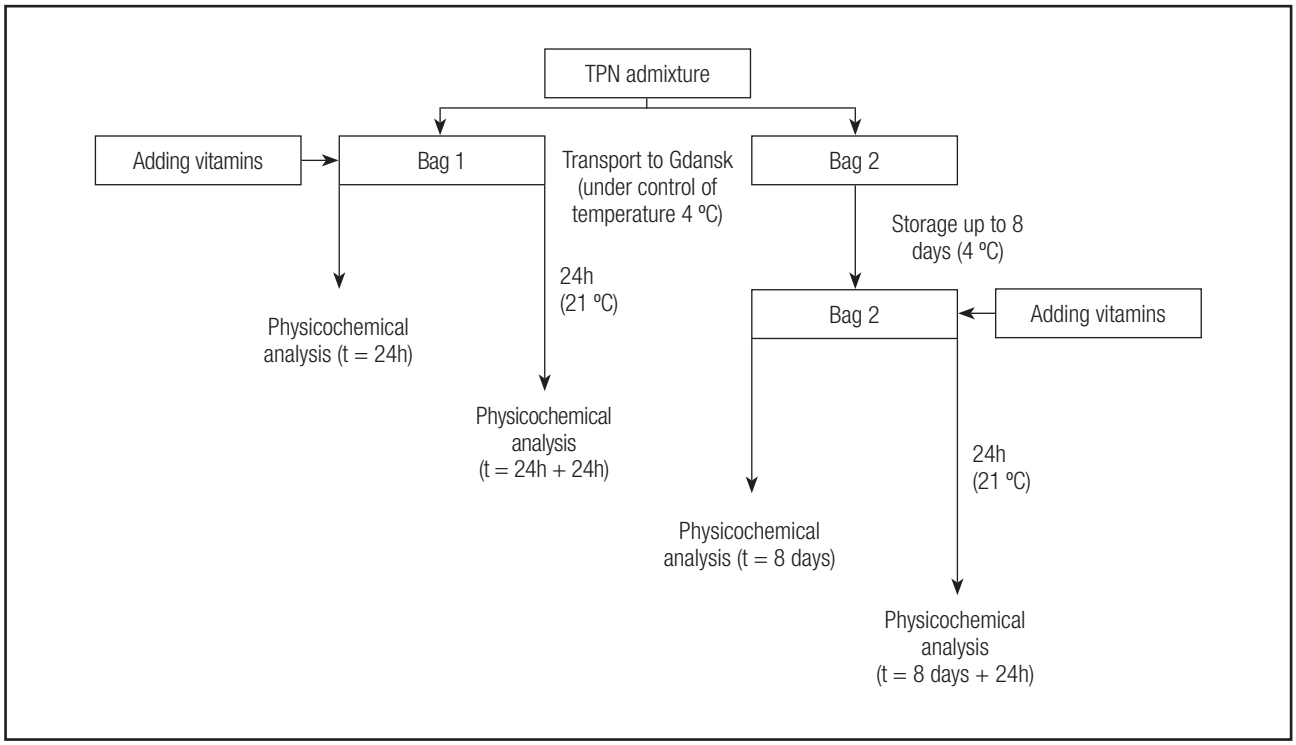

Figure 1.
Schedule of analysis of TPN admixtures.

size of ≥ 1 µm. Each microscopic sample (10 µl by a manual pipette) was analyzed with 40-fold magnification. Five individual visual fields were inspected per microscopic sample (15 total visual fields/aliquot): four in the corner and one in the middle of the preparation.

The size of the lipid droplets in the visual field was determined using an ocular micrometer (0.01 mm). The diameter of the largest lipid droplet was measured and counted in each of the 15 visual fields tested per aliquot. The diameter of the largest lipid droplet and the number of lipid droplets above 5 µm were measured and counted in each of the 15 visual fields tested per aliquot. The specifications of microscopic screening are shown in table II. Laser diffractometer method (LD) allows determining the median diameter ($d_{0.5}$ below this parameter is diameter of 50% of oily globules) and the maximum diameter of 90% of oily globules ($d_{0.9}$). Photon correlation spectroscopy method (PCS) was used to determine Z-average parameter.

RESULTS

VISUAL AND MICROSCOPIC OBSERVATIONS

Over eight days of storage, no visual changes were observed in the test samples stored at room temperature or in 4 °C. There was no creaming or discoloration. Neither precipitates nor flocculation were visible. A visual inspection was done for the assessment of large particle formation in the critical size 1-5 µm.

Under microscopic observation, the mean of the largest lipid droplet in µm out of 15 visual fields of 5 µm as the upper limit value for the emulsion stability was never reached by any sample, except one admixture (TPN 4). The mean value of the larger oily globules was about 2-3 µm (Table II and Fig. 2). There was no trend for the droplet size to increase or decrease over time of storage. In the unstable TPN 4 admixture, oil droplets in the range of 4-10 µm were detected.

OILY DROPLET SIZE DISTRIBUTION

Laser diffractometry method

Value of median ($d_{0.5}$) of oily droplets size in the complete admixtures was 310-390 nm and 90% of oily droplets ($d_{0.9}$) were under 570-680 nm. Despite the various composition and time of storage no oily globules lager than 1 µm were detected in any of all admixtures by using laser diffractometry method (Fig. 3).

Photon correlation spectroscopy

Z-average of oily droplets size was in range 252-372 nm, while the polydispersion index was 0.062-0.223, which indicates mo-

Table II. Microscopic observations of admixtures

TPN	t = 24h	t = 24h + 24h	t = 8 days	t = 8 days + 24h
1	Few 2 µm	Few 2 µm	Few 2 µm	< 1 µm
2	2 µm	< 1 µm	< 1 µm	< 1 µm
3	2 µm	2-3 µm	< 1 µm	2 µm
4	5-15 µm	10 µm	5-10 µm, agglomerates	Few 5-8 µm
5	2 µm	< 1 µm	Few 2 µm	2 µm
6	2 µm	Few 2 µm	< 1 µm	Few 2 µm
7	< 1 µm	2 µm	< 1 µm	< 1 µm
8	< 1 µm	< 1 µm	< 1 µm	< 1 µm
9	2 µm	< 1 µm	< 1 µm	< 1 µm
10	3-4 µm	2-3 µm	2-3 µm	Few 2 µm
11	< 1 µm	2-3 µm	Few 2 µm	2-3 µm
12	2-3 µm	2-3 µm	Few 2 µm	3-4 µm
13	2-3 µm	2-3 µm	Few 2 µm	2-3 µm
14	2 µm	2-3 µm	Few 2 µm	Few 2 µm
15	2 µm	< 1 µm	Few 2 µm	Few 2 µm
16	2 µm	2 µm	2-3 µm	Many 2-3 µm
17	< 1 µm	Few 2 µm	< 1 µm	Few 2 µm
18	2 µm	Few 2 µm	< 1 µm	Few 2 µm
19	2 µm	2 µm	2 µm	2 µm
20	2-3 µm	4-5 µm	2 µm	2-3 µm
21	2 µm	2 µm	2-3 µm	Few 2-3 µm
22	2-3 µm, few 4 µm	4-5 µm	2-3 µm	Many 4-5 µm
23	2-3 µm	4-5 µm	2 µm	2-3 µm
24	Few 2 µm	Few 2 µm	Few 2 µm	Few 2 µm
25	Few 2 µm	3-4 µm	2-3 µm	2-3 µm
26	2-3 µm	Few 3-4 µm	Few 2 µm	2-3 µm
27	Few 2 µm	Many 4-5 µm	Few 2 µm	Many 4-5 µm
28	2-3 µm	Few 2 µm	Few 2 µm	Few 2 µm
29	Many 2-3 µm	Few 2 µm	Few 2 µm	Few 2 µm
30	2-3 µm	2-3 µm	2-3 µm	2-3 µm

nodispersity studied systems (Fig. 4). The smallest oily droplets (Z-average approx. 250 nm) was recorded in admixtures 28, 29 and 30. No significant changes (± 30 nm) of oily droplets were noticed during storage TPN mixtures (Fig. 4). The TPN admixtures 2 and 10 have only at t = 24h larger oily droplets (Z-average about 550 nm), but in the others point of analysis Z-average was approximately 310 nm, so these admixtures were concluded as

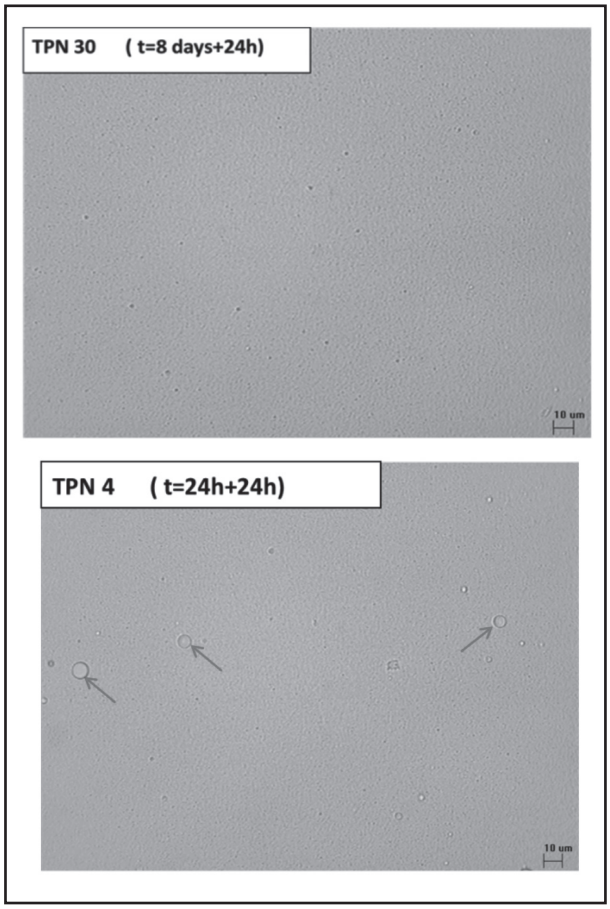

Figure 2.

Microscopic observation of admixtures (scale 10 µm).

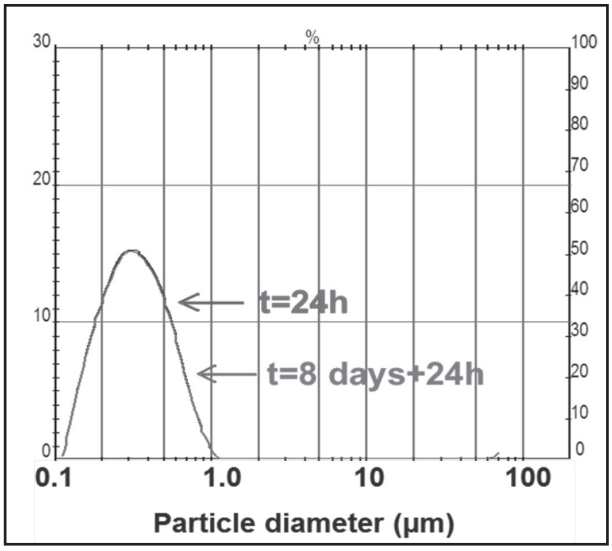

Figure 3.

Distribution of oily droplets of TPN 25 admixture during storage.

stable. Admixtures 7, 16, 22, 25 and 26 in a single time point reported a second peak in the range of 0.5 µm, indicating the presence of larger droplets of oil. However, the analysis in the other time points did not confirm these changes.

Zeta potential analysis

Zeta potential of all admixtures was in range -19 to -38 mV and did not change during the storage (± 4 mV) when compared with samples at t = 0 (Table III). The lowest recorded zeta potential of -40 mV was noted with TPN 23 while TPN 30 was seen to have a zeta potential of -21 mV (Table III).

pH measurement

The pH values in complete TPN admixtures were in range 5.29-6.29. Compared with samples at t = 24h, these values did not change (± 0.05 of units) during storage (Fig. 5). The smallest pH value (pH 5.3) of this parameter was observed in TPN 22, 25, 27, 30.

DISCUSSION

All TPN admixtures under investigation were prepared using standard procedures in the hospital Pharmacy. Due to clinical needs, admixtures contained a much higher than normal physiological concentration of electrolytes: calcium (3-10 mmol/l Ca^{2+}), magnesium (1-10 mmol/l Mg^{2+}) and potassium (7-60 mmol/l K^{+}) ions. CAN parameter of investigated admixtures was much higher than current in range 300-1400 mmol/l and CaxP (the products of multiplication of calcium and phosphate ions concentration) was in range 1-43 $mmol^2/l^2$. The highest CAN parameter was noticed in admixtures 30 (1402 mmol/l), whereas the smallest was found in admixtures 14 (322 mmol/l). All investigated admixtures were prepared using inorganic calcium salt to check if they are safe in PN for small children and if they can be used in clinical practice. Many authors suggest that calcium gluconate is preferred over calcium chloride when compounding PN because of its superior compatibility with inorganic phosphates. PN solutions containing calcium gluconate carry a higher aluminum load than equivalent solutions compounded with calcium chloride, leading to increased potential for aluminum toxicity (12). Premature infants are particularly at high risk of aluminum accumulation and toxicity as they often require days of PN support and have immature kidneys that are incapable of excreting aluminum efficiently. Calcium gluconate and phosphate salts are known to be especially high in aluminum content and are often administered to premature infants in substantial amounts to promote bone mineralization (13).

The analysis of physicochemical subjected to 30 TPN admixtures prepared in two bags in the Pharmacy of the Children's Memorial Institute in Warsaw. Incomplete (no vitamins) TPN admixtures were prepared in the single-chamber bags Exacta-Mix

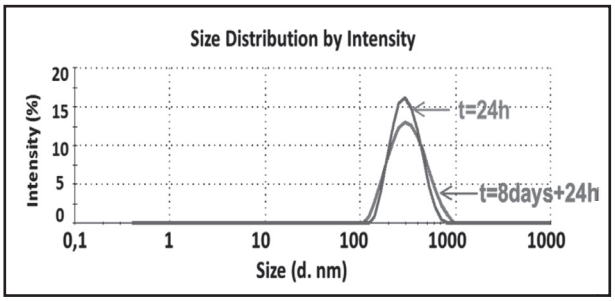

Figure 4.
Distribution of oily droplets of TPN 4 admixture during storage PCS method.

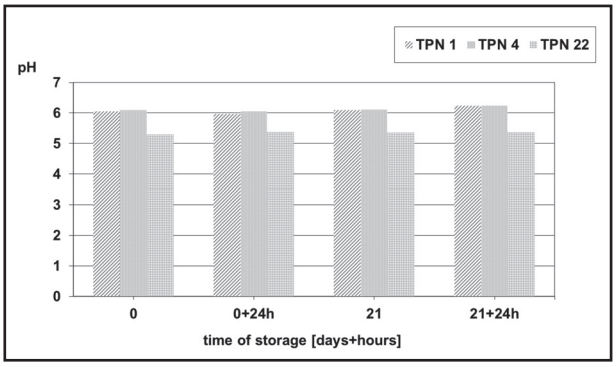

Figure 5.
pH values of the TPN admixtures, the effect of storage.

Eva bag Parenteral. Each composition of the TPN admixture was prepared in two bags, which allowed for analysis at four points: first bag, at t = 24, that is to say 24 hours after preparation (including transport), and after 24 hours of storage at room temperature (t = 24h + 24h); second bag, after eight days of storage at 4 °C (t = 8 days) and also after 24 hours storage at room temperature (t = 8 days + 24h).

The term physical stability of the TPN mixtures stored for a long time has practical application in parenteral nutrition at home: you can prepare the patient "inventory" of mixtures for a limited time. In the present study, the ability to store the mixtures tested to eight days was evaluated. The most important parameter to evaluate the physical stability of the mixtures is the presence of a drop of oil ≥ 5 µm, because they exceed the size of the diameter of capillaries and, consequently, if they are introduced into the bloodstream in large quantities, they can lead to embolism, necrosis of the surrounding tissues or have an effect on the functioning of the organ (14). It is believed that a small amount of oil with droplet sizes greater than 5 µm is not dangerous for the patients, since lipases are present in the endothelium of blood vessels. Lipases are responsible for the biodegradation of fatty acid esters. Among the test methods used, the most reliable, detecting drops of oil with increased size in mixtures TPN, turned out to be microscopic

Table III. Zeta potential (mV) of TPN admixtures

TPN	t = 24h	t = 24h + 24h	t = 8 days	t = 8 days + 24h
1	-28.5	-28.9	-30.7	-22.8
2	-32.2	-33.2	-34.3	-34.9
3	-29.2	-32.0	-37.5	-26.4
4	-30.6	-29.2	-35.2	-34.6
5	-32.0	-30.2	-39.2	-33.7
6	-32.1	-29.8	-33.3	-29.7
7	-31.6	-32.9	-33.5	-33.9
8	-28.0	-31.0	-31.6	-32.9
9	-28.6	-32.1	-32.2	-31.8
10	-24.8	-30.1	-24.4	-29.1
11	-32.0	-33.2	-31.6	-33.1
12	-30.8	-35.6	-30.6	-32.8
13	-33.9	-37.4	-36.9	-33.9
14	-36.6	-41.3	-37.7	-39.5
15	-34.4	-40.3	-34.6	-34.7
16	-33.7	-35.5	-32.8	-32.2
17	-31.2	-34.5	-34.2	-30.0
18	-32.5	-36.2	-32.0	-32.8
19	-32.3	-40.1	-36.1	-35.4
20	-32.2	-40.8	-31.3	-27.6
21	-31.6	-30.0	-34.0	-30.3
22	-28.5	-29.5	-35.1	-28.8
23	-38.2	-38.8	-43.9	-40.2
24	-32.3	-29.7	-31.5	-30.6
25	-28.3	-27.7	-29.6	-24.6
26	-22.9	-26.5	-29.4	-22.9
27	-27.5	-28.3	-28.1	-26.4
28	-28.1	-27.0	-28.5	-27.4
29	-28.5	-28.3	-30.2	-27.2
30	-22.5	-19.2	-23.3	-19.5

observation. The significance of this method to determine the durability of mixtures of the TPN also stress the authors of many publications. The light microscope method is highly sensitive and practicable, with a simple equipment and a conventional method validated by photon correlation spectroscopy (PCS) and the Coulter method (15). Using a microscope with a 40-fold magnification allows the detection of particles approximately 1 µm in size or enlarged emulsion particles up to 100 µm in size. Furthermore, other non-lipid globules (such as particulate matters or precipitations) can also be detected using this method. The method provides an easy, sensitive, cost-efficient, time-sparing, and convenient way to test the physical stability of a lipid emulsion in the critical droplet size to indicate destabilization (large fat droplet assessment ≥ 1-2 µm), and it is suitable for drug incompatibility testing in parenteral admixtures.

However, it is necessary to verify microscopic observation by other methods, so in this paper TPN admixtures were also analyzed using laser diffraction (LD) and photon correlation spectroscopy (PCS). Particle size measurement by means of a LD MasterSizer E enables the detection of particles from 0.05 to 80 µm, indicating size distribution. In turn, the use of ZetaSizer Nano ZS apparatus to measure the particle size using the method of dynamic light scattering allows the determination of particle size in the range of 0.6 nm-6 µm, taking advantage of the differences in the speed of the Brownian movement of particles in the medium in which they are suspended. The studies used both methods in view of the fact that, if the particles are too large, this method cannot determine the PCS size. An increase in oil droplet size by LD was not observed in any of the admixtures tested, despite their presence under microscopic observation. Some studies using PCS (no trends over time) detected the presence of a second peak and increased polydispersity index.

While mixtures 2 and 10 in the midpoint of the test (t = 24h) indicated an increased average droplet size of the oil phase (approximately 200 nm - by PCS), and mixtures 7, 20, 22, 25 and 26 showed the presence of a single time point of the second peak of about 5 mm, this change was not confirmed in the remaining time points. Although the results obtained by methods LD and PCS do not allow to detect irregularities at all the time points (the presence of larger oil droplets), yet on the basis of microscopic observations the mixture was physically unstable with composition 4. When the results obtained by the PCS and LD, it can be said that the median value of the oil droplets (Dv50; LD method) and an average oil droplet sizes (Z-Average, a method PCS) is slightly different. Z-average values were approximately 50 nm smaller. Measurement of zeta potential of TPN admixtures showed no significant changes during storage for 24h at room temperature (Table III). Zeta potential values were in the range denoted generally TPN admixtures. Another important factor indicating the stability of parenteral admixtures is pH, which decreases over time in PN admixtures because of the hydrolysis of fat triglycerides. Additional chemical reactions yielding base or acidic products also affect the pH. For the lipid stability and lecithin emulsifier, a pH range of 5-8 is necessary. The negatively charged surface (phosphate moiety) prevents the coalescence of the lipid globules. A pH below 5.0 favors lipid instabilities (16). In this study, no significant changes were noted in pH during storage of TPN admixtures (Fig. 5). Considerably lower pH of the mixtures 22, 25, 27 and 30 as compared to other systems is caused by using a different amino acid preparation (18 Vamin EF).

CONCLUSIONS

Based on the results of this study, and despite the increased concentration of electrolytes, the excess of CAN (297 to 1402)

and the presence of inorganic calcium salts, the physicochemical stability of the parenteral admixtures tested has been demonstrated. The exception was mixture 4, which was found to have coalescence of drops of oil visible during microscopic observations and at some point of time by the PCS, so the composition of TPN 4 should be modified. An important observation was that inorganic calcium salt in PN can achieve the same stability profile as the organic salt in use in the clinic today. To apply the above examined compositions in clinical practice is their preparation under the same conditions using the same ingredients and packaging. Changing any factor (packaging, manufacturer, or replacement of the inorganic salt to organic) can cause a lack of physical stability and requires reconsidering physical stability. The research of physical stability indicates that, except for admixture 4, the test compositions can be used in nutrition at home with prolonged stability of prepared TPN admixtures, provided that they are implemented in the same manner and using the same components.

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