



Original/*Pediatría*

Nutritional Support Teams: the cooperation among physicians and pharmacists helps improve cost-effectiveness of home parenteral nutrition (HPN)

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Abstract

Introduction: Modern home parenteral nutrition (HPN) requires the preparation of tailored admixtures. The physicians' demands for their composition are often at the variance with pharmaceutical principles, which causes the necessity of either the preparation of *ex tempore* admixtures or stability testing ensuring long shelf life. Both approaches are not cost-effective. The aim of the study was to use the cooperation among physicians and pharmacists to assure both: cost-effectiveness and patient-tailored HPN admixtures.

Methods: The first part of the study consisted of the thorough analysis of prescriptions for the most demanding 47 HPN patients (27 females and 20 males, mean age 53.1 year) treated at one HPN center to create few as possible long-shelf life admixtures. The second part of the study consisted of stability testing and modifications.

Results: The analysis showed over 137 variations needed to cover all macro- and micronutrients requirements. Their cost as *ex-tempore* solutions was extremely high (over 110 000 EURO/month) due to logistics and similarly high if stability test for variation were to be performed (68 500 EURO). Therefore prescription was prepared *de novo* within team of physicians and pharmacists and four base models were designed. Water and electrolytes, particularly magnesium and calcium showed to be the major issues. Stability tests failed in one admixture due to high electrolytes concentration. It was corrected, and the new formula passes the test. Five basic models were then used for creation of new bags. Cost of such an activity were 3 700 EURO ($p < 0.01$)

Conclusions: The cooperation within the members of nutritional support team could improve the cost-effectiveness and quality of HPN.

EQUIPOS DE ASISTENCIA NUTRICIONAL: LA COOPERACIÓN ENTRE MÉDICOS Y FARMACÉUTICOS AYUDA A MEJORAR LA RENTABILIDAD DE LA NUTRICIÓN PARENTERAL DOMICILIARIA (NPD)

Resumen

Introducción: La nutrición parenteral domiciliaria (NPD) moderna requiere la elaboración de preparados a medida. Las peticiones de los médicos en cuanto a la composición de estos preparados muchas veces difieren de los principios farmacéuticos, lo que suscita la necesidad de elaboración de preparados *ex-tempore* o unas pruebas de estabilidad que garanticen el almacenamiento a largo plazo. Estas estrategias no resultan rentables. El objetivo del estudio consistió en utilizar la cooperación entre médicos y farmacéuticos para asegurar tanto la rentabilidad, como la elaboración a medida de los preparados NPD.

Métodos: La primera parte del estudio consistió en el análisis pormenorizado de las prescripciones para los 47 pacientes con una NPD más exigente (27 mujeres y 20 hombres, edad media 53,1 años) tratados en un centro NPD para crear el menor número posible de preparados de larga duración. La segunda parte del estudio consistió en pruebas de estabilidad y modificaciones.

Resultados: El análisis demostró que eran necesarias más de 137 variaciones para cubrir todas las exigencias de macro y micronutrientes. Su costo como soluciones *ex-tempore* resultó extremadamente elevado (más de 110.000 EUROS/mes) debido a la logística, e igualmente alto en caso de requerirse una prueba de estabilidad (68.500 EUROS). Así, la prescripción fue preparada *de novo* por el equipo de médicos y farmacéuticos y se diseñaron cuatro modelos básicos. Las dificultades principales fueron el agua y los electrolitos, en particular magnesio y calcio. Las pruebas de estabilidad fracasaron en uno de los preparados debido a la alta concentración de electrolitos. Esto fue corregido, y la nueva fórmula superó la prueba. A partir de ahí se emplearon cinco modelos básicos para la creación de nuevas bolsas. El costo de esta actividad supuso 3.700 EUROS ($p < 0.01$)

Conclusiones: La cooperación entre los miembros del equipo de asistencia nutricional puede mejorar la rentabilidad y la calidad de la NPD.

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Abbreviations

AiO: all in one.
EVA: Ethylene vinyl acetate.
HPN: home parenteral nutrition.
MCBs: multi-chamber bags
NST: Nutritional Support Team.
PN: parenteral nutrition.

Introduction

Parenteral nutrition (PN) requires the intravenous provision of all essential nutrients: proteins, energy, electrolytes, vitamins, trace elements and water¹. PN was introduced into medical practice in 1968 in the United States and it was considered the fourth milestone in surgery after antisepsis, antibiotics and anesthesia². It has become a widely available and recognized method of treatment used in case of the feeding via the gastrointestinal tract is impossible, insufficient or contraindicated³. If a patient requires long-term parenteral nutrition, it is possible to start it on the home basis – it is the home parenteral nutrition (HPN). The main indication for home parenteral nutrition is the intestinal failure, independently on the etiology. The latter include short bowel syndrome, mechanical or paralytic obstruction, dysmotility, fistula, a congenital defect, or malabsorption^{4,5}. The most recent European survey reported the prevalence of 2-40 per million and an incidence of 4-6 per million per year for home parenteral nutrition in patients with benign primary diseases, with 35% having short bowel syndrome⁶.

HPN is usually delivered in as few servings per day as possible, in an overnight and cyclical manner, to improve patients' quality of life as much as possible^{4,6}.

The key factor determining the efficacy and safety of parenteral nutrition is the pharmacologically stable and patient-tailored intravenous admixture. The quality of HPN depends on many factors, such as the composition of the regimen, its relevance for the patient's medical condition, the method for its preparation, the safety and accuracy of the process, and the pharmacological stability of the admixture⁷. Home-based preparation of parenteral nutrition has once been the only option, but it is now more the historical perspective than reality, however still in use in some countries, as it is a high-risk process providing patients with a low quality of life and a lot risk. Multi-chamber bags represent alternative option, but because of their limited availability, the best standard may only be assured by admixtures prepared at the pharmacy unit

Palabras clave: *Nutrición parenteral domiciliaria. Composición. Rentabilidad. Garantía de calidad. Estabilidad física. Equipos de asistencia nutricional.*

with compounding system. They should be delivered to patients' home afterwards with a vehicle dedicated for that purpose, ensuring the proper conditions of transportation. The patients' daily need for nutrients, electrolytes, vitamins and trace elements physicians has been determined by the ESPEN guidelines and must take into account the initial nutritional status of the patient and co-morbidities⁸. Due to the large number of ingredients of PN and their range of concentration, there is theoretically an infinite number of combinations and permutations of regimens that could be requested by physician. However, in practice, the standardization of admixtures has offered opportunity to manage aseptic conditions during preparation and an effective workload⁶. Pharmaceutical principles (GMPs), which ensure the resistance to adverse processes occurring during the preparation, storage, transportation, or the administration, limit the possibility to individualize nutrient doses. That type of approach is possible only if admixtures are prepared on daily basis (so called *ex tempore* admixtures) as the stability of drugs for parenteral administration consists of microbiological stability and physicochemical properties⁷. HPN can be managed that way, but costs of such treatment are extremely high, because bags have to be delivered every day. The latter is also a reason for the relative low quality of life, as patient or care-giver collects PN solutions every day.

There is also another solution to that problem, which is the enabling long shelf life by stability tests for 7, 14 or even 30 days. The testing process is composed of two parts: microbiological and physicochemical evaluation. The latter determines the shelf life, and it is defined by the pharmacological activity of its ingredients. This activity cannot decrease below a value of 10%, moreover, solutions must be free from toxic degradation products. The major stability and compatibility issues can be divided as follows: physicochemical stability of the lipid emulsions, precipitation of chemical components mainly as calcium and phosphate interactions, and stability and compatibility of vitamins⁷.

As those examinations have to be performed in case of any prescription modification and single cost is at least 500 EURO, they are very expensive and strongly affect the cost-effectiveness of HPN.

Aim of the study

The aim of the study was to use the cooperation among physicians and pharmacists, who were members of Nu-

tritional Support Team (NST) to improve the quality of patient-tailored HPN and to limit the costs of home nutrition.

Materials and Methods

The study was conducted in two steps: 1) - clinical evaluation of PN admixtures composition and selecting of standard formulation and 2) – physical testing of the stability of PN admixtures.

Part 1

Analysis of PN prescriptions

The study was performed between January 2011 and April 2012 in the group of 135 HPN at Stanley Dudrick's Memorial Hospital in Skawina, Poland. 47 patients of those, (27 females and 20 males, mean age 53.1 year), were found to be receiving multi-chamber bags (MCBs, n=11) or all-in-one (AiO, n=36) admixtures and additional intravenous electrolyte-containing infusions. The latter ensured the appropriate provision of electrolytes, which could be added to neither AiOs nor MSBs due to impending instability. Patients' characteristics were presented in Figure 1 and 2. All patients signed informed consent.

NST analyzed thoroughly all regimens of all 47 patients. The number of variations necessary to ensure tailored delivery was calculated. The cost of logistics was assessed.

PN formulations were analyzed in regards to their macronutrients (amino acids, glucose, lipid emulsion), micronutrients (trace elements, vitamins and electrolytes) and water content per day afterwards. Consequently, based on those findings, four model formulas were planned. The assumption was made that the logistics had to be limited down to one delivery per week not only to decrease costs, but more importantly to fulfill patients and caregivers' expectations, as the quality of life questionnaire, performed previously, showed that the preferable delivery rate was once a week.

Therefore, new formulas were supposed to undergo tests to ensure safety ranges presented in table I. Those tests guaranteed required 16-day physicochemical stability when stored at 2-8°C, along with 24 hours at room temperature after injection of vitamins and trace elements (added minutes before infusion).

Part 2

Preparation

All new admixtures were manufactured at the Hospital Pharmacy Unit using an automated admixing device Baxa EM 2400 (Baxa Corporation, Englewood, CO, USA) supported by PN calculator Abacus version 2.1. The following components of TPN were commercially avail-

able as sterile and apyrogenic solutions: Aminoplasmal 10% (B. Braun Melsungen AG, Germany), Glucose 40% (B. Braun Melsungen AG, Germany), Lipofundin MCT/LCT 20% (B. Braun Melsungen AG, Germany), Water for Injection (B. Braun Melsungen AG, Germany), Sodium chloride 10% (B. Braun Melsungen AG, Germany), Potassium chloride 15% (Fresenius Kabi AB, Sweden), Magnesium sulphate 20% (Polpharma, Poland), Calcium chlorate 10% (WZF, Poland), Glycophos (organic phosphate containing solution of sodium glycerophosphate, Fresenius Kabi AB, Sweden), Addamel (trace elements, Fresenius Kabi AB, Sweden), Vitalipid N Adult emulsion and Soluvit N lyophilisate for solution (Fresenius Kabi AB, Sweden). All components were placed into final delivery container (ethylene vinylacetate bag, EVA). Admixtures were prepared in two different series, in each two bags were collected. One sample was supplemented with vitamins immediately after preparation, while the other was not. In the second series vitamins were added to both samples. Bags were stored and protected from sun light under controlled temperature of 4±1°C for 16 days after labeling. Four hours before the analysis pre-admixtures were transferred to room temperature, and vitamins (Soluvit N dissolved in Vitalipid N Adult) were added. This step was carried out under non aseptic conditions to simulate home conditions, in which admixtures are prepared by caregivers or nurses.

Physical analysis of complete TPN admixtures

Physical analysis was done by Department of Pharmaceutical Technology of Medical University of Gdansk. Procedures for the stability test were presented in fig.3. Physical analysis of complete admixtures was carried out after 24 h (4±1°C) storage of admixtures (t=24h) – time needed to transport from the Hospital Pharmacy to Gdansk and after 24 h of storage at room temperature, with light protection (t=24h+24h). The second bags of pre-admixtures were examined immediately after adding vitamins after 16 days of storage at 4±1°C (t=16 days) and after 24 h and 48h of storage at room temperature, with light protection (t=16days+24h, t=16days+48h). Complete admixtures were subjected to physical stability analysis consisting of visual inspection, microscopic observation (optical microscope with camera B1 223A Motic, Wetzlar, Germany), pH measurement (pH-meter Orion 350, Beverly, USA, with combination electrode), zeta potential measurement (Zetasizer Nano ZS, Malvern Instruments, Malvern, UK) and determination of oily globules size distribution (laser diffractometer – LD, MasterSizer E Malvern Instruments, Malvern, UK and photon correlation spectroscopy – PCS, Zetasizer Malvern Instruments, Malvern, UK). Laser diffractometry method allows determining the median diameter (d0.5 - below this size is a diameter of 50% of oily globules) and the maximum diameter of 90% of oily globules (d0.9) whereas PSC method allow to determine Z-average of oily droplets.

Table I
Composition [g/L] of TPN admixtures and CAN parameters

TPN	1	2	3	3a	4
Glucose 40%	136.4	145.8	142.4	142.4	141.4
Aminoacids	34.1	35.0	35.6	35.6	35.9
Lipid emulsion	29.1	27.5	29.5	29.6	30.3
Nitrogen	5.5	5.6	5.7	5.7	5.7
Na ⁺ [mmol/L]	72.7	75.0	75.8	75.8	82.8
K ⁺ [mmol/L]	72.7	75.0	75.8	75.8	82.8
Ca ²⁺ [mmol/L]	7.27	6.67	7.58	6.06	6.90
Mg ²⁺ [mmol/L]	7.27	6.67	7.58	6.06	6.90
Phosphate [mmol/L]	18.1	20.8	18.9	18.9	24.1
CAN [mmol/L]	1096	1022	1138	1060	944

Statistical analysis

The data were analyzed on an intention-to-treat basis with the SPSS v.16 (SPSS Inc., Chicago, IL) software package. The differences in proportions among groups were evaluated using the Chi-square test. Continuous data were analyzed using the Mann–Whitney U test. A p value < 0.05 was accepted as being statistically significant.

Results

Part I

The analysis of 47 patients PN prescription showed 137 various diet modifications needed for the safe and efficient HPN. The most frequently used diets were presented at Table I.

The analysis showed also that 16% of patients required additional supplementation of calcium and 43% magnesium during HPN. The calculated amount of those electrolytes reached up to 10 mmol per day, and had to be supplemented by the use of additional intravenous fluids.

It became clear that previously used formulas neither covered patients' needs nor guaranteed pharmaceutical stability. The cost-effectiveness of changes needed to improve the situation was analyzed next. Two options were considered by NST: ex-tempore manufacturing and stability testing for all necessary PN variations. Both were proven to be equally ineffective in term of cost:

- The simulation showed the mean cost of those AiOs prepared as ex-tempore solutions, of over 110000 EURO/month due to logistics: every day delivery.
- Stability testing for all possible variations would have reached approximately 68 500 EURO.

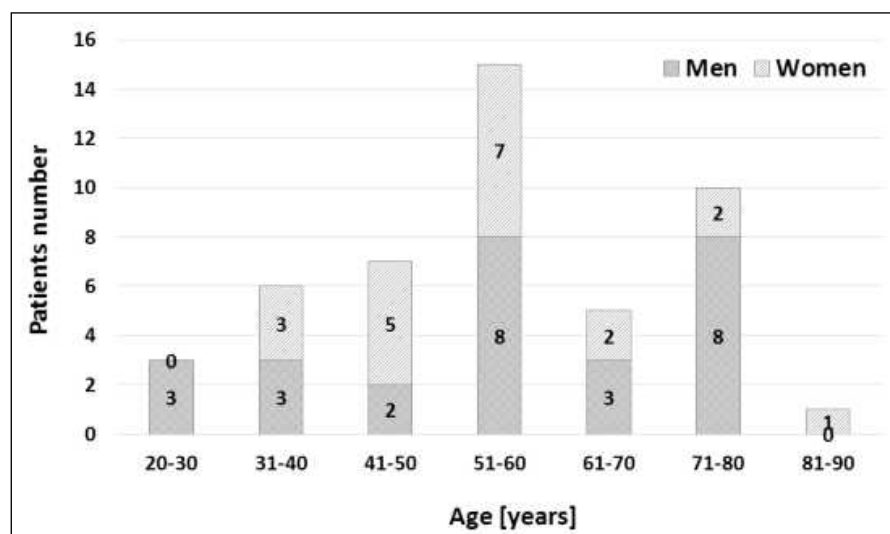


Fig. 1.—HPN study population.

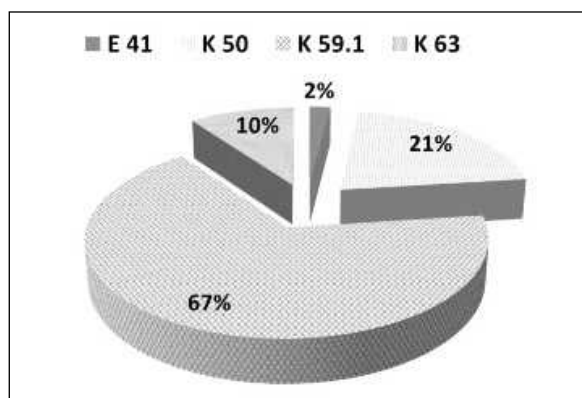


Fig. 2.—HPN classification diseases in the study population.

As both measure were unacceptable on grounds of cost-effectiveness, NST decided to test the hypothesis that it was possible to design long shelf-life model diets with wide safety nutrients range, which could be used for new admixtures afterwards without the necessity for new stability tests. The hypothesis assumed exceeding Critical Aggregation Number (CAN) of PN solutions. As CAN represents one of the most critical rules that must be followed, all necessary safety tests had to be performed.

NST's members prepared four model PN formulas (numbered 01-04) with increased content of calcium, magnesium and reducing water content. The value of Critical Aggregation Number (CAN) in all admixtures exceeded 600 mmol/L. As calcium glubionate was not commercially available due to drug shortage, so it must be replacement with the inorganic calcium chloride had to be used (Table I).

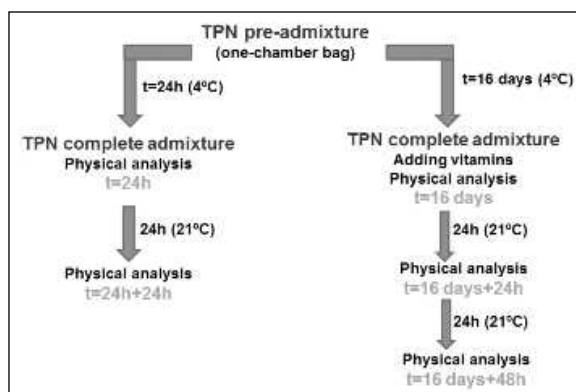


Fig. 3.—Scheme of physical analysis of complete TPN admixtures.

Part 2

Visual and microscopic observations

Subsequently, all admixtures underwent thorough testing as describes above. During the visual check-out all admixtures were homogenous and no creaming was observed after 24 and 48 hours storage at the room temperature. During microscopic observation most of the complete admixtures were characterized by size of oily globules not larger than $1 \mu\text{m}$, which are safe for patients (Figure 4). Larger oily droplets about $6 \mu\text{m}$, up to $10 \mu\text{m}$ were noticed in complete admixture TPN 3 just after 24h at room temperature (Figure 5). Those were noticed in two batches, hence the admixture number 3 was described as unstable and sent for revision.

The calcium and magnesium content in the unstable AiO was reduced and the revised TPN 3 composition was analyzed again. The size of oily globules in modified ad-

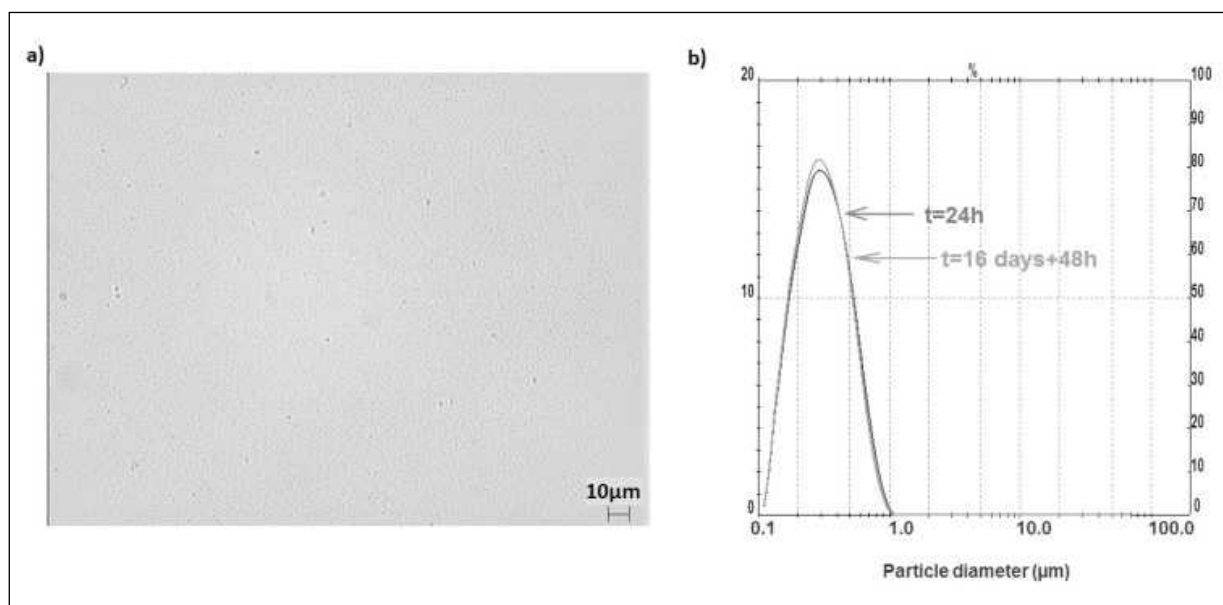


Fig. 4.—Complete TPN admixture 3a - microscopic observation (scale $10 \mu\text{m}$) at $t = 16 \text{ days} + 48\text{h}$ (a) and size distribution of oily droplets (b).

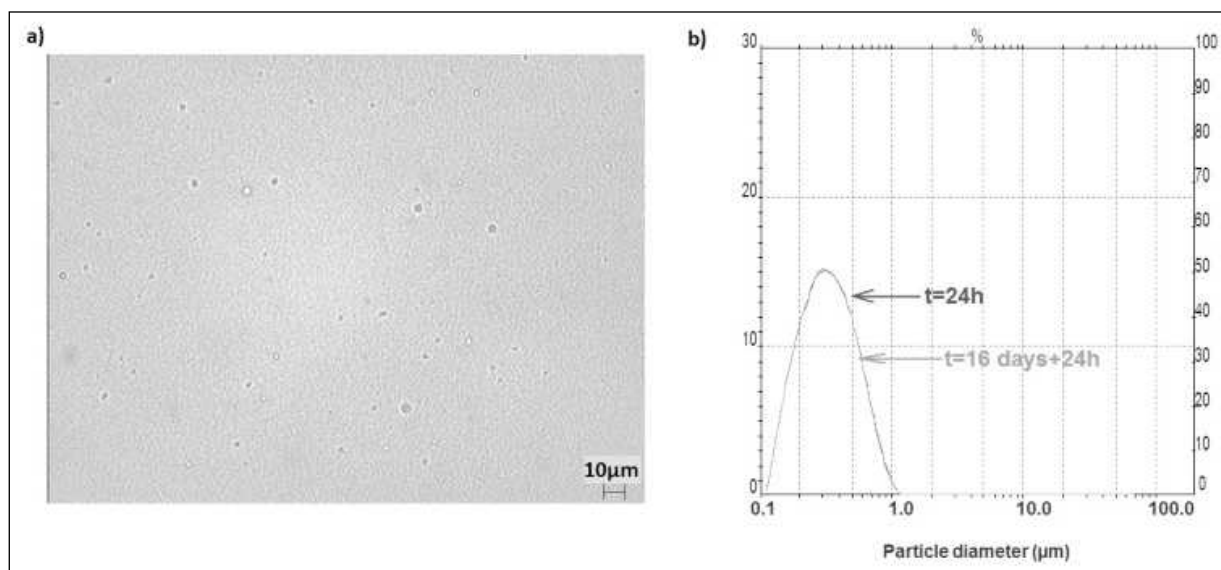


Fig. 5.—Unstable TPN admixture 3 - microscopic observation (scale 10 μm) at $t=24\text{h}$ (a) and size distribution of oily droplets (b).

mixture TPN 3a was smaller than 1 μm (Figure 4) and no destabilization was observed during the storage.

The detailed pharmaceutical data are presented below:

Oily droplet size distribution

a/ Laser diffractometry method

No oily globules larger than 1 μm were detected in any of admixtures using laser diffractometry method (Figure 4 and 5). Mean ($d_{0.5}$) oily droplets size was 290-310 nm and 90% of oily droplets ($d_{0.9}$) were under 530-590 nm (Figure 6). Oily droplets size did not change after storage for 24h and 48h of complete admixtures at room temperature (Figure 4). It was noted that time of storage of pre-admixtures without vitamins in one-chamber bags

had no influence on droplet size distribution (Figure 5). No differences were noticed between stable and unstable TPN admixtures (3 and 3a, see above) in detection of oily droplets size using laser diffractometry (Figure 4 and 5).

b/ PCS method

Z-average parameter measured using PCS method was between 250-295 nm despite various compositions (Figure 7). Slight changes during storage of TPN admixtures were observed but they were not significant ($p < 0.05$).

Zeta potential

The zeta potential observed in admixtures was negative and ranged from -21.5 to -24 mV (Figure 8). Des-

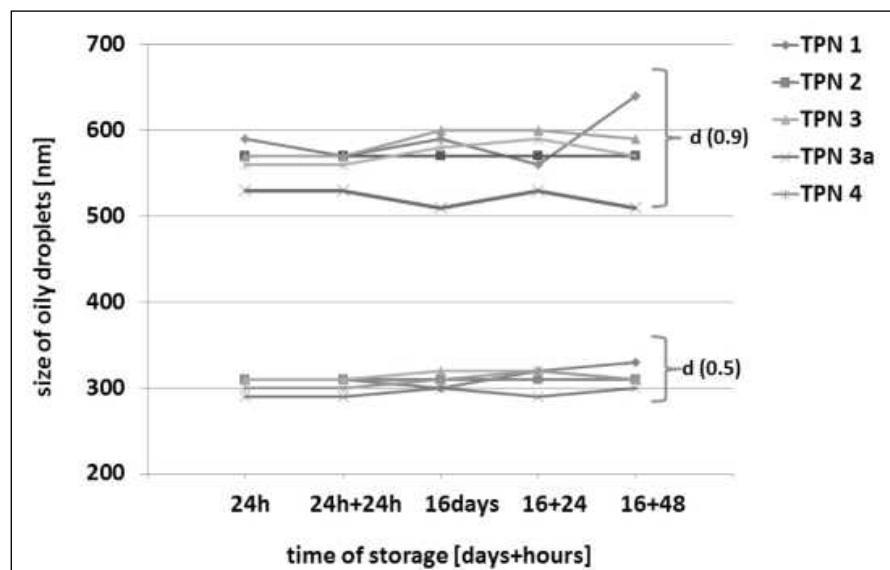


Fig. 6.—Size of oily droplets [nm] of TPN admixtures - the effect of storage.

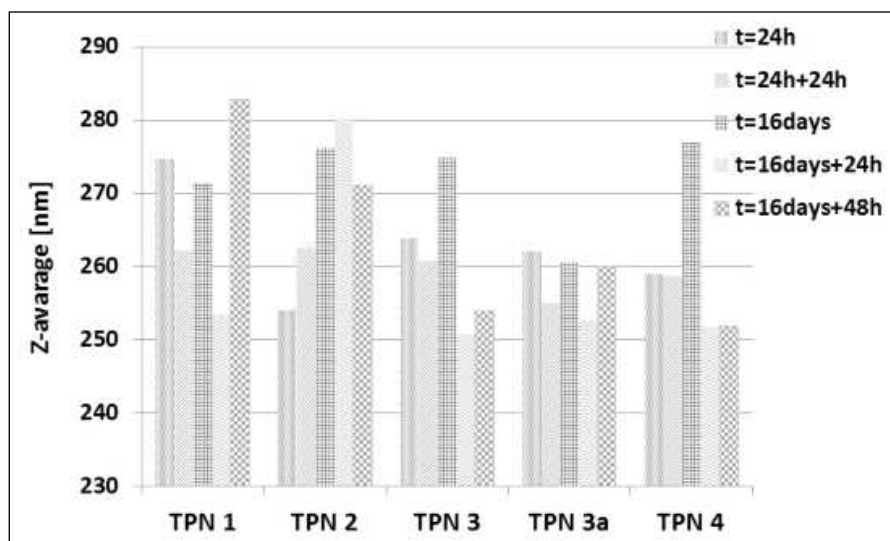


Fig. 7.—Z-average parameters of TPN admixtures - the effect of storage.

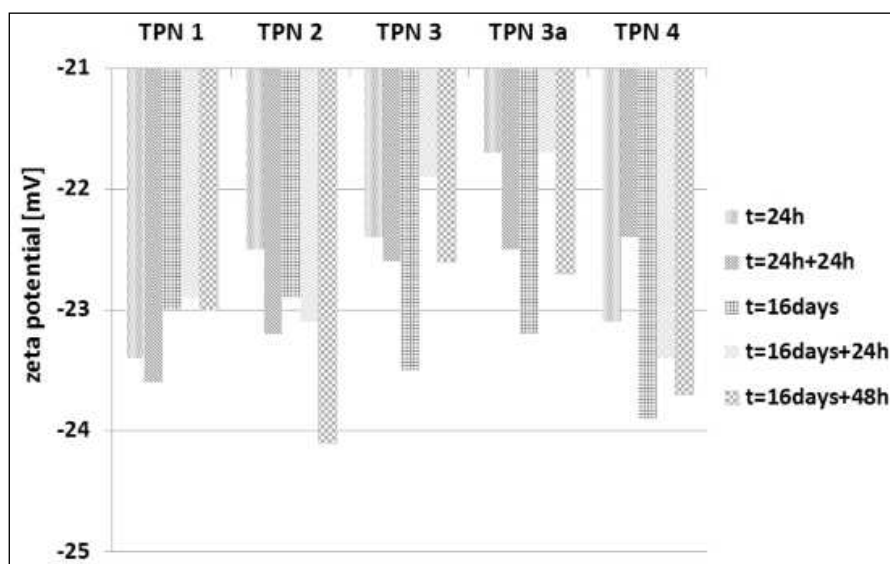


Fig. 8.—Zeta potential of the complete admixtures - the effect of storage.

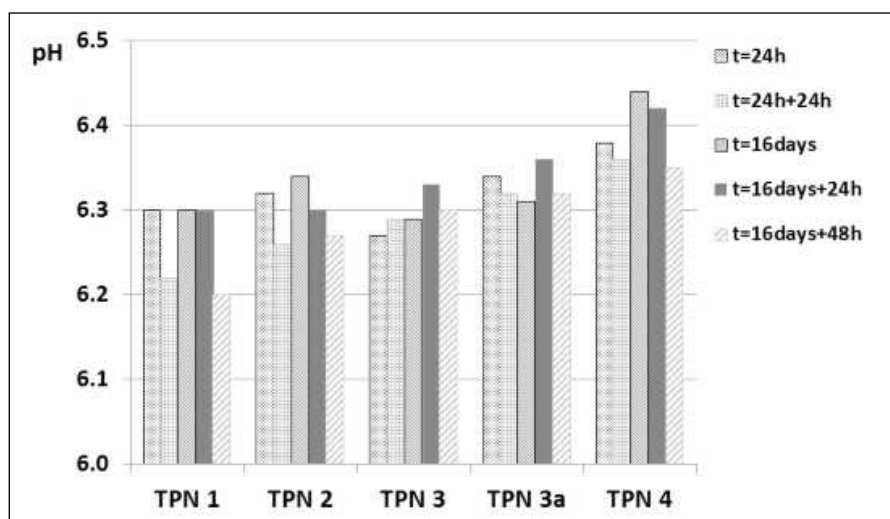


Fig. 9.—The pH values of the complete admixtures - the effect of storage.

pite various compositions of admixtures, only small changes in zeta potential were observed.

pH measurement

The pH values in TPN admixtures ranged between 6.2 – 6.5 and did not change during storage (Figure 9).

Microbiological stability

Microbiological stability was tested after 16 days of storage under controlled temperature of $4\pm 1^{\circ}\text{C}$ and 24 h of storage at the room temperature in accordance with the monograph European Pharmacopeia concerning sterile parenteral formulations. The mixtures were sterile during time of storage and administration.

Cost effectiveness

The cost of stability tests needed for proving all new AiO admixtures reached 2 500 EURO. Cost of PN components, HPN bags, and workloads used for that process was 1 200 EURO.

Cost of all procedures needed for the creation of new admixtures reached 3,700 EURO and were significantly lower than simulated costs presented above ($p < 0.01$).

An additional gain in regards to cost-effectiveness, was the use of four just created formulas for all new coming patients, which reduced future charges to zero.

Discussion

AIO admixtures are complex formulations with limited stability and narrow shelf life. The key factor determining the efficacy and safety of parenteral nutrition is the pharmacologically stable and patient-tailored intravenous admixture. The quality of HPN depends on many factors, such as the composition of the regimen, its relevance for the patient's medical condition, the method for its preparation, the safety and accuracy of the process, and the pharmacological stability of the admixture, as described above.

Costs of HPN include mostly costs of the admixtures (substrates, workloads, pharmaceutical examinations, etc.), everyday care (physicians and nurses surveillance), laboratory tests and imaging modalities and logistics. It is also compulsory nowadays to fight for the improvement of patient's quality of life. The most important issues of HPN comprise AiO admixtures (size, volume, content) and the delivery. One has to deal with those problems effectively to provide valuable and safe PN. Those aims may sometimes, however, be at the variance and hence it is important to enable HPN teamwork.

It is even more complicated if someone realizes that a typical admixture is composed of about 40-50 components and it is an oil-in-water emulsion. The lipid emulsion is the most sensitive part of TPN. Its use must meet specific requirements. The size of fat globules should be similar to natural chylomicrons, with a physiological upper limit of particles size at about $5\ \mu\text{m}$. The stability of the lipid emulsion is maintained by mechanical and electrostatic repulsive forces counteracting the coalescence of small oil droplets dispersed by an emulsifying agent. Surrounding medium pH, electrolytes, trace elements, and other additives may reduce the repulsive forces among the particles resulting in emulsion destabilization⁹⁻¹². An important factor influencing physical stability of fat particles is critical aggregation number (CAN). CAN is associated with cationic concentrations at which lipid particles aggregate. Calculation of the CAN is accomplished using the following formula: $\text{CAN} = a + 64b + 729c$, where *a* stands for monovalent, *b* for divalent, and for trivalent cations molar concentrations. This measure equals to the total amount of cations and it should be less than $600\ \text{mmol/L}$ ^{7,9}. It should be noted, however, that the value of CAN is strictly theoretical, and the stability of the lipid emulsion is affected by many additional factors, so it is possible to exceed the CAN while the stability of emulsion is maintained.

As proven above, NST work succeeded in the creation of new formulas, able to cover demands of all patients. Value of CAN in all tested admixtures was greater than 600 (in range 944-1138, Table I), because of high calcium and magnesium concentration ($6.1-7.6\ \text{mmol/L}$). In microscopic observation all, except for one, complete TPN admixtures were characterized by oily globules not larger than $1\ \mu\text{m}$, which are safe when intravenously administered. Only one complete admixture (TPN 3) was unstable because of oily globules size of about 6 up to $10\ \mu\text{m}$ (Figure 4) and had to be modified.

The unintended presence of precipitation and toxic products can cause various negative consequences for the patient. This can range from thrombophlebitis up to multi-organ failure. Adverse effects of drug incompatibilities extend periods of patients' hospitalization and the total costs^{13,14}. Therefore a long term quality assurance of admixtures in HPN is very important. Investigation, testing and quality control of parenteral nutrition are analytical challenges. Tests are expensive and time-consuming. Standardization of PN formulations could be helpful to limit the cost of stability analysis's, risk of pharmaceutical instability and to meet the most needs of patients. The goal cannot be achieved, however, only by the pharmacists. The cooperation between physicians and pharmacists is necessary to achieve that goal as aims of both groups are often contraindicating. Physicians demand high electrolytes content with a small volume to improve patient's quality of life, while pharmacist have to ensure the stability of admixture.

The following study proved that following even rigorous pharmaceutical principles for the admixtures preparation might not limit physicians in the creations of patient-tailored admixtures. New PN are available in the described HPN center since August 2012. Actually, there are no patients, who require additional supplementation of calcium or magnesium as extra infusions during HPN.

Conclusions

Only the cooperation and mutual understanding and trust between physicians and pharmacists allow achieving a successful nutritional therapy. It was proven obvious that NST actions allow improving outcome and cost-effectiveness, and they should be recommended for every HPN center.

Conflict of interest

The authors hereby declare that the article is original, is not under consideration for publication anywhere else and has not been previously published. Moreover, the authors declare no potential or actual personal, political or financial interest in the material, information or techniques described in the paper.

Statement of authorship

All authors state that all authors have made substantial contributions and final approval of the conceptions, drafting, and final version of the manuscript.

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