CLINICAL SCIENCE OF NUTRITION
Case Report
Clin Sci Nutr 2019; 1(3): 141-3 • DOI: 10.5152/ClinSciNutr.2019.910

Stability problems of pediatric parenteral nutrition solutions

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Cite this article as: Kelleci Çakır B, Paloğlu G, Karababa Ç, Demirkan K, Yiğit Ş. Stability problems of pediatric parenteral nutrition solutions. Clin Sci Nutr 2019; 1(3): 141-3.

ABSTRACT

Parenteral nutrition (PN) must be considered an intravenous medication, containing over 50 ingredients and additives. Thus, the stability of the final product is always under risk. PN can be received in two ways: from a ready-to-use bag or from an individually tailored bag, both in adults and in pediatric patients. Pediatric PN admixtures are more susceptible than adult PN admixtures due to their nature. Patients who receive PN often need to receive parenteral medications concomitantly, and separate administration is challenging most of the time. Here we report two problems with stability encountered with pediatric PN bags. In the first case, the main focus is on the compatibility of heparin with PN. Compatibility of the medications via the Y-site or a three-way stopcock must be examined in such cases. If the medication is incompatible with PN, administration via the Y-site or addition into the PN mixture should be avoided. Emulsion disruption caused by heparin is a known example of incompatibility for pediatric PN. In the second case, the main focus is on the additives and their amount in the pediatric PN mixture. Compounding pediatric PN is mixing numerous additives in a small volume, which results in a highly concentrated solution that often causes calcium–phosphate precipitation. This may lead to serious consequences, including death. All the possible causes of instability, even the temperature of the environment, must be considered. In pediatric PN solutions, the cooperation between physicians and pharmacists is necessary for maintaining safe nutritional treatment.

Keywords: Clinical nutrition, clinical pharmacy, drug administration, incompatibility, parenteral nutrition

Introduction

Parenteral nutrition (PN) can be provided in two ways: from a ready-to-use bag or from an individually tailored bag, both in adults and pediatric patients. Using a standard, commercial, formulation has some advantages with regard to minimizing procedural incidents, and on the other hand, it does not always meet the nutritional needs of most patients. For pediatric patients, there are very limited bag options with a certain amount of energy and proteins provided. To secure individual patient requirements, tailored PN formulations are preferable in newborns, infants, and children (1, 2). Stability of the final product is always an obligatory consideration. PN is an intravenous medication, with more than 50 ingredients and additives (3). All these ingredients, additives, the order in which they are added, ways of delivery, and environmental characteristics influence the overall PN admixture stability. Stability means that the admixture maintains the same status throughout the preparation and infusion time. The clinically important and very susceptible components to instability are the lipid emulsions, the reaction of calcium–phosphate, vitamins, and trace elements. The instability reactions are influenced mostly by the addition of drugs and electrolytes, but also by the storage material and the environmental conditions such as the presence of oxygen, exposure to ultraviolet light, pH value, and high temperature (4).

Here, we report 4 cases in which two different types of stability problems occurred with PN solutions that were compounded for infants in our university pediatric hospital in a 1-week period (29 December 2016–02 January 2017).

Case Presentations

Stability problem 1

Event notification reports were sent to the Clinical Pharmacy Department by the Hospital Quality Assurance Unit on January 12, 2017, about dissociation observed on the

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Submitted: 23.05.2019 **Accepted:** 03.10.2019

upper side of the PN bags of 3 infant patients and detected by the nutrition support team nurses. After the evaluation by clinical pharmacists, it was observed that the contents and the concentrations in the label of PN bags were appropriate, except admixing 125–130 unit heparin to all three PN solutions. As an example, one of the patient's PN ingredients is provided in Table 1. The dissociation detected in these PN solutions was explained by the heparin-induced lipid instability.

Stability problem 2

An event notification report was sent to the Clinical Pharmacy Department by the Hospital Quality Assurance Unit on March 3, 2017, regarding the precipitation formation in the PN solution of 1 infant patient, which was detected by nutrition support team nurses. The contents and their concentrations in the label of PN bags were also evaluated by clinical pharmacists, and it was found that due to metabolic disorders, the PN solution was prepared without amino acids (Table 1). A lower final volume and higher pH value were expected in PN solutions without amino acids, which leads to a higher risk of calcium and phosphate interactions and precipitation in the solution. The precipitation detected in this PN solution was explained by the calcium–phosphate interaction due to increased pH and decreased volume of the final PN solution.

Table 1. Ingredients of parenteral nutrition solutions

	Stability problem 1 (mL)	Stability problem 2 (mL)
Amino acid (Primene®)	63	0
Dextrose 10%	91	0
Dextrose 20%	134	0
Dextrose 30%	0	150
Dextrose 50%	0	10
Lipid (Clinoleic®)	25	48
Sodium chloride 3%	15	26
Potassium chloride	5	0
Photassium phosphate	0	3
Calcium gluconate	12.5	8
Multivitamin (Slouvit®)	2.5	3
Multivitamin (Vitalipit®)	10	10
Heparin	125 unit	130 unit
Total volume	350	260

Discussion

Patients receiving PN often need to receive parenteral medications concomitantly; however, separate administration is not possible in practice for most of the patients. If another catheter is not available, some medications can be added to PN solutions, such as insulin or H2-receptor blockers according to the literature, and for other medications, compatibility via the Y-site or a three-way stopcock must be examined. If the medication is incompatible with the PN solution, this may result in various visual incompatibilities (e.g., emulsion disruption caused by heparin in the presence of calcium) (4, 5).

At many centers, mostly to maintain catheter patency and sometimes to decrease infections and hypertriglyceridemia, heparin is regularly added at a dose of 0.5–1 unit/mL to neonatal PN solutions (6, 7). Heparin causes solution destabilization through binding of divalent cations and influences the integrity of the emulsion (8, 9). When the irreversible destabilization (such as coalescence and oiling out) occurs, PN bags must be disposed immediately. The literature suggests that low doses of heparin are unlikely to destabilize PN solutions; however, more studies are needed to clarify this (10-13).

In the cases with Stability Problem 1, it was concluded that heparin was the only component that could be responsible for dissociation of these PN solutions. Although it was added within the limits indicated in publications (7), it was suggested that clinicians need to be more careful about adding heparin to PN bags due to stability problems, and if the patient needs higher doses of heparin, it should be administered via different catheter for patients receiving lipids in PN solutions.

Another concern about compounding pediatric PN is mixing numerous additives in a small volume that results in a highly concentrated solution often causing calcium–phosphate precipitation. This may have serious consequences, including death. The underlying physical and chemical factors responsible for an incompatibility between these ions can be the pH of the admixture, choice of salt type, amino acid concentration, mixing sequence, and infusion temperature (14).

In the cases with Stability Problem 2, it was concluded that calcium–phosphate precipitation was formed due to lack of amino acids in the PN solution, which leads to an increased pH of the solution. Besides, the lack of amino acids in the PN solution also leads to decreased final volume of the PN solution, resulting in calcium–phosphate precipitation because of higher concentrations of calcium

and phosphate. Therefore, it was suggested to apply either calcium or phosphate separately from PN solutions in patients who should not receive amino acids in PN solutions due to their clinical condition.

In addition, during the evaluation period, it was documented that the average room temperature in the newborn unit was between 25°C and 28°C degrees. Storage and environmental temperature may also have an effect on the stability of PN solutions, especially for calcium–phosphate precipitation. Therefore, to keep the room temperature under control in such a critical department was also suggested.

In conclusion, since PN solutions have a very sensitive stability due to over 50 ingredients, the preparation and application of PN solutions must be carried out carefully. If it is known that the drug is incompatible or under unknown compatibility condition, these drugs should never be added to the PN admixture or be infused via the Y-line. On the other hand, physical examination is important during the preparation, storage, and administration of PN solutions, and it should be kept in mind that precipitates may be masked due to lipid emulsions. The risk of calcium–phosphate precipitation formation should be especially considered in pediatric PN solutions, and the cooperation between physicians and pharmacists is necessary in such scenarios. While physicians demand a high electrolyte content with a small volume, pharmacist must ensure the stability of admixture. A multidisciplinary team approach may be required to maximize the impact of nutrition support service and to provide a safe and proper PN treatment to the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.K., K.D.; Design - Ş.Y., K.D.; Supervision - Ş.Y., K.D.; Resources - B.K., G.P., Ç.K.; Materials - B.K., G.P., Ç.K., K.D.; Data Collection and/or Processing - B.K., G.P., Ç.K.; Analysis and/or Interpretation - B.K., G.P., Ç.K., K.D.; Literature Search - B.K., K.D.; Writing Manuscript - B.K., K.D.; Critical Review - Ş.Y. K.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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