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REVIEW ARTICLE

Physical Stability of Commonly Used Medication Administered by Parenteral Nutrition Admixtures in Hospital: A Systematic Review

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Abstract

Background: Inpatients requiring parenteral nutrition (PN) often need to receive intravenous medication, but physical instability can occur between medications and PN. This review aimed to bring together the available literature on the physical stability of medication with PN used in hospitals. Methods: We conducted a systematic electronic literature search of PubMed, Science Direct, and SpringerLink during the period 2009-2019 for all English language research publications evaluating the physical stability of commonly used medication administered by PN in hospital. Results: Out of 88 studies, 7 studies selected for this review. From all studies conducted in this review found 14 combinations of drugs that are not compatible with PN admixtures, including levetiracetam, albumin, amoxicillin, cefepime, esomeprazole, fluorouracil, pantoprazole, tropics, trace elements, vitamins, and vancomycin. For adding medications directly to the PN solution, specific criteria should be considered, such as physicochemical properties of the ingredients and drug concentration. Conclusion: The stability of IV medications and PN is an important concern in delivering safe and effective medication and nutritional therapy. The role of healthcare professionals is needed to avoid this incident so that patient safety can be guaranteed.

Keywords: *Parenteral nutrition, Drug, Medication, Stability, Physical.*

Introduction

Parenteral nutrition (PN) is an important therapeutic modality for infants, children, and adults with a variety of indications [1].In addition, PN is a high-alert medication with a complex medication use process. Severe patients normally need PN that is given along with a variety of intravenous medications. It is sometimes difficult to follow the recommendation of strict avoidance of co-administration of the medications with PN, such as co-administration of medications with PN can be needed mainly in case of limited venous access. Nevertheless, physical instability can occur between medications and PN.

For example, due to the formation of precipitations and lipid droplet sizes that are too large can delay in recovery of inpatients. Besides that, it can also cause negative effects, namely death [2]. Therefore, to avoid clinical problems resulting from instability between the medications and PN, so a literature review studies are needed. The objective of this review was to provide information about the physical stability conditions of commonly used medication administered by PN in hospitals, including vitamin, and trace elements. Vitamin and trace elements are necessary to meet the nutritional needs of patients receiving PN. This information is expected to be useful for personnel who were mixing medications, vitamin, and trace elements with PN.

Methodology

Search Strategy

We performed a search in PubMed, Science Direct, and Springer Link (January 2009-

December 2019) for published articles in the English language. The search method consists of a search term for a systematic review. We used the search terms ["parenteral nutrition" or "total parenteral nutrition"] and ["drug" or "medication] and ["incompatibility" or "compatibility" or "stability"] and "intravenous or parenteral"] and ["patient"] and ["administration"]. All search terms were also used as free search terms mentioned in the abstract or title of the study. We aim to identify all studies related to the physical stability of drugs with PN in their research to collect information.

Study Selection

All original studies assessing physical stability between medication and PN published in English with a time frame year from 2009 until 2019 are selected for this review. Studies had to report incompatibility between medication and PN as an outcome. On the other hand, exclusion criteria were used: (1) letters; (2) review articles; (3) comments; (4) articles are not available in full text or abstract only, and (5) articles were related stability study of iv drug only. The PRISMA diagram of selected studies, summarizing study selection can be seen in Figure 1.

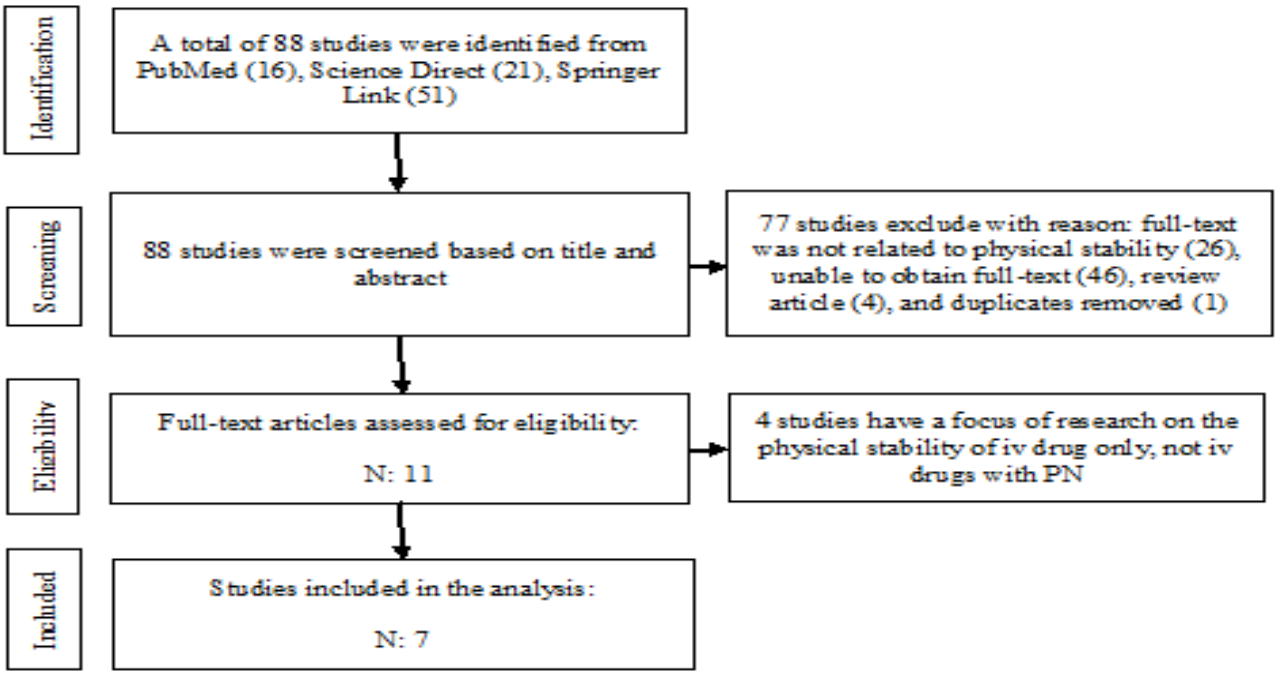

Figure 1: PRISMA diagram of retrieved studies

Data Extraction

Physical stability data of combinations between medication and PN were collected by two authors using a data extraction form. The data extraction form included the methodology and the result. The authors focus on data relating to physical stability test methods and the results of stability tests between drugs and PN. Test results highlighted by the authors include discoloration, phase separation, precipitate formation, lipid droplet size, PFAT5, and pH determination. Disagreement on the data is resolved by the discussion among the authors.

Study Quality Assessment

The study quality is done by two authors based on the STROBES checklist.

Result

Study Selection

The initial search of electronic databases resulted in 88 titles. After the initial selection by two authors, 77 articles were excluded (full-text was not relevant [n=26]; unable to obtain full-text [n=46]; review article [4]; duplicates [n=1]) and 11 articles were eligible to obtain that suitable for the topic desired by the author. Nevertheless, 4 articles have a focus of research on the physical stability of IV drug only. Finally, seven articles completely related to the study object and underwent data extraction. Data extraction was carried out by two authors using data extraction forms, including physical stability test methods and the results of stability tests between drugs and PN.

Study Characteristic

As shown in Table 1, six studies were conducted in the Europe continent and the last one was conducted in American continent. In European, the study was done in Switzerland [3,4], England [5], Poland [6-8]. Then In America, the study was done in Brazil [9].

Table 1: Characteristics of included studies

Author, Year	Country	Medication	PN	Test Methods	Duration	Stability
Aeberhard et al, 2017	Switzerland	Levetiracetam (LV)	PN with lipid	Visual, Light Microscopic, pH meter	168 hours	LV is not recommended to be mixed with PN containing lipid after 96 hours
Bouchoud et al, 2012	Switzerland	Albumin, Amoxicillin, Calcium chloride, cefepime, cyclosporine, esomeprazole, fentanyl, fluorouracil, furosemide, magnesium sulfate, meropenem, metoclopramide, metronidazole, midazolam, morphine sulfate, noradrenaline, octreotide, ondansetron, pantoprazole, paracetamol, piperacillin, potassium phosphate, tacrolimus, tropisetron, vancomycin	Lipid-free PN, PN with lipid	Colorimeter, Visual, Light Microscopic, Light Obscuration, pH meter	4 hours	Albumin, trophetron, amoxicillin, esomeprazole, and pantoprazole are not recommended to be mixed with PN containing lipids. High concentrations of fluorouracil, esomeprazole, and pantoprazole are not recommended to be mixed to lipid-free PN, while for amoxicillin and cefepime provided their use is no more than 1 hour after mixing.
Greenhill et al, 2019	England	Epinephrine, Milrinone, Vasopresine, Calcium gluconate	Lipid-free PN	Visual, pH meter	4 hours	Four drugs are recommended to be given with lipid-free PN
Stawny et al, 2019	Poland	Ampicillin	PN with lipid	Visual, dynamic light scattering, pH meter	144 hours	Co-administration of AMP in the same bag with TPN admixture at the tested dose is possible when used extempore and with light protection.
Watrobska - Swietlikowska et al, 2019	Poland	Furosemide, Torasemide	PN with lipid	Visual, light biologic microscope, pH meter	24 hours	Co-administration of furosemide or torasemide in the same bag with TPN admixture at the tested dose is possible
Lobo et al, 2012	Brazil	Trace Elements and Vitamins	PN with lipid	Visual, dynamic light scattering, light obscuration, pH meter	168 hours	Trace elements and vitamins can be given with PN no more than 24 hours at room temperature
Stawny et al, 2019	Poland	Vancomycin (VMC)	PN with lipid	Visual, dynamic light scattering, pH meter	4 hours	Avoidance of simultaneous administration of VMC with PN admixtures based on lipid emulsions containing olive oil, since this type of emulsion was found less stable and prone to form agglomerates when combined with VMC

All of the included studies asked about the incompatibility between PN and medications. PN used in the included studies contained lipids or not. And then, 100% of studies looked at the physical stability of PN admixture for> 4 hours

Test Methods of Physical Stability

In most studies using multiple methods to assess physical stability. The physical stability assessed mainly included discoloration, phase separation, presence of precipitates, lipid droplet size, $PFAT_5$, and pH determination. Visual inspections for discoloration, phase separation, and presence of precipitates. Discoloration was observed visually using black and white backgrounds in 2 (29%) studies. Visual inspections for discoloration without the aid of tools was found in 4 (57%) studies and 1 (14%) study using the colorimeter method (14%).

Furthermore, visual inspection to observe the occurrence of precipitation or not with the help of black and white background was found in 3 (43%) studies, without a black and white background in 3 (43%) studies, while visual inspection of phase separation was found in 7 (100%) studies. Visual inspection becomes very important to detect signs of physical instability, this can be seen from all studies always done to guarantee the quality of PN admixture [3-9]. The pH value was measured using a pH meter in 7 (100%) studies. Changes in pH over time were measured in all stability studies. Furthermore, $PFAT_5$ was measured using light obscuration in 2 (29%) studies. One study used light diffraction (14%).

Lipid droplet size was measured using microscopic light in three (43%) studies, other studies (57%) used dynamic light scattering (DLS). DLS is the most suitable for the detection of small droplets, in the nanometer size range, and less accurate for droplets with diameters above 1 mm [10]. The method used in all studies is still recommended by USP 38/NF 33 [11].

Physical Stability Data

The physical stability of the medications is summarized in Table 2. Of the 60 combinations for which stability data were available, 14 (23, 3%) were found to be unstable combinations. Forty-six combinations (76, 7%) showed no change in physical stability, either in terms of color, phase separation, precipitation, lipid droplet size, $PFAT_5$, and pH parameters. The summary provided in the table of this review took into consideration information on the concentration of drugs, can be seen in Table 2.

Table 2: The physical stability of the medication with PN

No	Medications	Type of PN		Physical Stability					
		Lipid-Free PN	Lipid PN	Discoloration	Phase Separation	Precipitation	Lipid Droplet Size	$PFAT_5$	pH
1	Levetiracetam 0,16%		√	**A (after 96 hours)**	NA	NA	NA	N	NA
2	Albumin 20%		√	NA	**A**	**A**	**A**	**A**	**A**
3	Albumin 20%	√		NA	NA	NA	N	N	N
4	Amoxicillin 5%/Ac. clavulanic 1%		√	NA	NA	NA	NA	NA	**A**
5	Amoxicillin 5%/Ac. clavulanic 1%	√		**A**	NA	NA	N	N	N
6	Calcium chloride 0,13 mmol/ml Ca		√	NA	NA	NA	NA	NA	NA
7	Calcium chloride 0,13 mmol/ml Ca	√		NA	NA	NA	N	N	N
8	Cefepime 10%		√	NA	NA	NA	NA	NA	NA
9	Cefepime 10%	√		**A**	NA	NA	N	N	N
10	Cyclosporine 0,25%		√	NA	NA	NA	NA	NA	NA
11	Cyclosporine 0,25%	√		NA	NA	NA	N	N	N
12	Esomeprazole 0,08%		√	**A**	NA	NA	NA	NA	NA
13	Esomeprazole 0,08%	√		**A**	NA	NA	N	N	N
14	Fentanyl 0,005%		√	NA	NA	NA	NA	NA	NA
15	Fentanyl 0,005%	√		NA	NA	NA	N	N	N
16	Fluorouracil 2,5%; 5%		√	NA	NA	NA	NA	NA	NA
17	Fluorouracil 2,5%; 5%	√		NA	NA	**A**	N	N	N

18	Furosemide 0,02-1%		√	NA	NA	NA	NA	NA	NA
19	Furosemide 1%	√		NA	NA	NA	N	N	N
20	Magnesium sulfate 0,4 mmol/ml Mg		√	NA	NA	NA	NA	NA	NA
21	Magnesium sulfate 0,4 mmol/ml Mg	√		NA	NA	NA	N	N	N
22	Meropenem 5%		√	NA	NA	NA	NA	NA	NA
23	Meropenem 5%	√		NA	NA	NA	N	N	N
24	Metoclopramide 0,5%		√	NA	NA	NA	NA	NA	NA
25	Metoclopramide 0,5%	√		NA	NA	NA	N	N	N
26	Metronidazole 0,5%		√	NA	NA	NA	NA	NA	NA
27	Metronidazole 0,5%	√		NA	NA	NA	N	N	N
28	Midazolam 0,25%		√	NA	NA	NA	NA	NA	NA
29	Midazolam 0,25%	√		NA	NA	NA	N	N	N
30	Morphine sulfate 0,5%		√	NA	NA	NA	NA	NA	NA
31	Morphine sulfate 0,5%	√		NA	NA	NA	N	N	N
32	Noradrenaline 0,1%		√	NA	NA	NA	NA	NA	NA
33	Noradrenaline 0,1%	√		NA	NA	NA	N	N	N
34	Octreotide 0,0025%		√	NA	NA	NA	NA	NA	NA
35	Octreotide 0,0025%	√		NA	NA	NA	N	N	N
36	Ondansetron 0,2%		√	NA	NA	NA	NA	NA	NA
37	Ondansetron 0,2%	√		NA	NA	NA	N	N	N
38	Pantoprazole 0,08%		√	**A**	NA	NA	NA	NA	NA
39	Pantoprazole 0,08%	√		**A**	NA	NA	N	N	N
40	Paracetamol 1%		√	NA	NA	NA	NA	NA	NA
41	Paracetamol 1%	√		NA	NA	NA	N	N	N
42	Piperacillin 8%		√	NA	NA	NA	NA	NA	NA
43	Piperacillin 8%	√		NA	NA	NA	N	N	N
44	Potassium phosphate 0,12 mmol/L PO_4		√	NA	NA	NA	NA	NA	NA
45	Potassium phosphate 0,12 mmol/L PO_4	√		NA	NA	NA	N	N	N
46	Tacrolimus 0,01%		√	NA	NA	NA	NA	NA	NA
47	Tacrolimus 0,01%	√		NA	NA	NA	N	N	N
48	Tropisetron 0,1%		√	NA	NA	NA	NA	**A**	NA
49	Tropisetron 0,1%	√		NA	NA	NA	N	N	N
50	Vancomycin 1%		√	NA	NA	NA	NA	NA	NA
51	Vancomycin 1%	√		NA	NA	NA	N	N	N
52	Epinephrine 0,01%	√		NA	NA	NA	N	N	NA
53	Milrinone 0,1%	√		NA	NA	NA	N	N	NA
54	Vasopressine 1 unit/ml	√		NA	NA	NA	N	N	NA
55	Calcium gluconate 10%	√		NA	NA	NA	N	N	NA

56	Ampicillin 10%		√	NA	NA	NA	NA	N	NA
57	Trace Element (Cu 0,2, Cr 0,002, Mn 0,02, Zn 0,5 µg/ml)		√	**A (after 24 hours)**	**A (after 24 hours)**	N	NA	NA	NA
58	Vitamin (A 1,3, D 5, E 10, B1 3, B2 3,6, B3 40, B5 15, B6 4, B7 60, B9 400, B12 5, C 100 µg/ml)		√	**A (after 24 hours)**	**A (after 24 hours)**	N	NA	NA	NA
59	Torasemide 0,01-0,045%		√	NA	NA	NA	NA	N	NA
60	Vancomycin 0,37%		√	NA	NA	N	**A (PN contained olive oil)**	N	NA

Information:
NA : Not Altered
A : Altered
N : Not Known

Discussion

For medications to be administered together with PN admixtures, they must be at least physically compatible. This systematic review identifies the physical stability of commonly used medication co-administered with PN in the hospital. This is very important because the paucity incompatibility data may have implication on patient safety in hospitals [2].We found published reports of fatal for combinations of drugs that are not compatible with PN can cause pulmonary embolism even to death [1, 2, 12].

Fourteen medications were incompatible with PN admixtures, with details nine medications were incompatible with lipid PN and five medications were incompatible with lipid-free PN. Five indicators were observed by researchers include discoloration, phase separation, presence of precipitation, lipid droplet size, $PFAT_5$, and pH for lipid PN mixtures, whereas for lipid-free PN mixtures only 3 indicators were observed namely discoloration, phase separation, and presence of precipitation. The indicators observed in all studies are in accordance with ASPEN and USP recommendations [3-9].

Furthermore, we observed variations related to the duration of observations among physical stability studies. More than 43% of studies observed the physical stability of PN mixing for> 1 day and 57% of studies were only observed for 4 hours. The duration of this observation can be considered when determining the duration of administration of drugs with PN. This discoloration was considered an indicator of incompatibility between amoxicillin, cefepime, proton pump inhibitors (PPIs), and lipid-free PN. It is known that they are prone to degradation in an acidic solution [4,13].

Furthermore, levetiracetam is incompatible with lipid PN after 96 hours at 37°C which is marked by discoloration [3]. Meanwhile, trace elements and vitamins were incompatible with lipid PN after 24 hours at room temperature (25°±3°C) and body temperature (40±3°C) that are showed by discoloration and phase separation [9]. Nevertheless, they were compatible with lipid PN until the study was completed at the refrigerator (4°±3°C).

This study is in line with previous research that trace elements (zinc, manganese, copper, chromium) in TPN mixtures remained stable after 24 h of storage at room temperature or 4°C [14, 15]. Vitamins are commonly to be among the least stable ingredients in PN mixtures because vitamins can easily be degraded under particular conditions such as exposure to daylight, the type of plastic used to manufacture the PN container and infusion equipment, and storage temperature [15].

Storage temperatures can increase the rate of drug degradation, this is evidenced in research conducted by Maiwada and Said [16]. Therefore, it can be recommended that vitamins or trace elements be added immediately before administration or that administration should be commenced within 24 of addition. In which case the addition is usually done by ward staff, without pharmaceutical control.

In addition, to avoid degradation during storage and control during administration by minimizing direct daylight exposure. Another factor indicating the instability of PN is the presence of precipitation. Precipitation was detected in lipid PN with 5-fluorouracil (5-

FU). This is related to the poor solubility of that medication substance at pH values was still basic (pH 8.3) [4]. For weakly basic drugs it will be more soluble in acidic conditions (in an ionized form), and vice versa. Also noted that salt-form drugs, generally more soluble than drugs in the form of acids and bases [10].

The occurrence of precipitation in certain preparations can have an impact on increasing the size of lipid droplets and $PFAT_5$, as in the study of an admixture of albumin 20% and tropisetron with PN lipids. Most drug incompatibilities are a manifestation of acid-base changes. Base solutions added to the acidic solutions can certainly change the degree of acidity of mixtures [17].

Significant pH changes can cause changes in the charge on the micelle's surface. This change in charge impacts the phase separation in the lipid emulsion system [8]. A decrease in pH was detected in PN lipids with amoxicillin (pH 7,9 to pH 7,6) [4]. The pH decreases over time because of the hydrolysis of fat triglycerides [3].

Based on the description, pH measurement is an important factor to consider before mixing PN, because pH can be used to explain or predict drug incompatibility. PN admixtures containing olive oil are incompatible with vancomycin, so it is recommended to avoid giving vancomycin with PN containing olive oil. Olive oil contains monounsaturated fatty acids (one unsaturated carbon bond) about 85% more than fish oil, soybean oil and coconut oil.

In addition, Psomiadou reported that olive oil contains quite a lot of antioxidants around 10-37 mg/100 g [18]. Therefore, this type of oil is less stable and forms agglomerates with vancomycin [8, 19-25]. Some drugs are incompatible with PN, however if forced drugs and PN are needed by critical patients, it is recommended for separate administration with PN. This review may help healthcare professionals decide whether an administration of medications with PN is possible. This information may help to implement complex therapeutic schemes in practice when co-administration is unavoidable. There are several limitations to this review. These are valid only for the medication concentrations and duration tested in the included studies of this review as this parameter is an important factor for pharmaceutical preparation stability. In addition, there may be published compatibility studies in other languages besides English, so there are other drugs commonly used in other countries that are not included in this review.

Conclusion

Most of the reviewed article concerns drug administration with PN admixtures but without considering chemical stability and the results are limited to the classical parameters of physical stability for commonly used medications co-administered with PN in hospital. The results described in this review should be approached with caution before mixing the medication with PN admixtures like considering the physicochemical properties of the ingredients and drug concentration. The availability of comprehensive physical stability data is a very important step to facilitate the pharmacist's work and improve patient safety.

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