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Quality and safety of parenteral nutrition for newborn and preterm infants as an on-ward preparation

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ABSTRACT

Background For newborn and preterm infants, standardised and individual parenteral nutrition (PN) is used. PN preparation is at risk for contamination and dosing errors. The quality of PN is crucial for infants and has a direct impact on their health status and safety.

Purpose The aim of this study is to evaluate the physicochemical and microbial quality of PN for newborn and preterm infants prepared on a neonatal ward.

Methods Sampling of various individual PN prepared by nurses on a neonatal ward was performed. Formulations included maximal four electrolytes, variable dextrose and amino acid concentrations. Depending on the sample volume, up to three quality analyses were performed: (1) test for bacterial endotoxins by kinetic-chromogenic method, (2) sterility according to the European and US Pharmacopoeia, and (3) quantification of electrolytes by capillary electrophoresis and of dextrose by ultraviolet detection after enzymatic reaction of hexokinase. The concentrations obtained were evaluated based on the US and Swiss Pharmacopoeia specifications for compounded preparations and compared to the widened pharmacy specifications.

Results The composition of 86% of the 110 analysed PN prepared by nurses on the neonatal ward corresponded to their medical prescription. 14% were out of the acceptable widened pharmacy ranges. We found no microbial contamination in the samples. All PN were free from endotoxins.

Conclusion Component concentrations of PN prepared on wards by nurses differed frequently and significantly from their medical prescription, and the deviation can be critical depending on the component and its mode of action. The sample size is too small to evaluate the microbial contamination.

INTRODUCTION

All over the world, there are different strategies of managing parenteral nutrition (PN) for newborn and preterm infants. The practices concerning the prescription, preparation, handling and administration of PN vary from one hospital to another.[1] PN standardisation increases the quality of PN and the security of the patients.[2 3] Nevertheless, there is still no common opinion on whether or not to standardise PN for neonatal patients, as individual PN can be more adapted to the patients' needs.[4]

Even though guidelines[5–7] do exist, they are not always followed by prescribers. Frequently, neonatologists define their own limits and procedures (eg, osmolarity).[8] Another reason for non-compliance to these guidelines is the clinical status (eg, unstable blood values) and medical complications (eg, venous access) of patients.[4]

PN is usually prepared at hospital pharmacies as a 'centralized preparation', but at some hospitals PN is still prepared on ward by nurses.[3] This is the case in two Swiss hospitals and in 20% of French hospitals.[9] A European survey performed in 2010 by Bouchoud *et al*[10] showed that 12% of PN are prepared on hospital wards. The requirements for the preparation area, the personnel's training and the quality control regarding intravenous medication preparation including PN vary greatly.[3] Hospital pharmacies mostly follow the current 'EU guidelines to Good Manufacturing Practice' (GMP)[11 12] and are obliged to apply the guidelines of the 'Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme' (PIC/S)[13] for health system establishments, so they must produce in laminar airflow hoods in clean-rooms with validated operators. Hospital wards do not need to follow these guidelines. They are not always in possession of laminar airflow hoods to assure a clean preparation and they are not equipped and trained to realise quality controls.

Medicine preparation and administration are known to be at risk for nosocomial infection[3 4 14] as PN preparation may include more than 10 raw products and administration is mainly done by central venous access.[3 15] Following the death of three neonatal patients in the hospital of Chambéry in 2014 caused by PN contamination,[16] a national enquiry concerning paediatric PN (PPN) practices has been conducted.[9] The report (2015) included several recommendations to increase the security of these preparations. Beneath others, the IGAS (Inspection Générale des Affaires Sociales) proscribed PN preparation on hospital wards and determined the pharmaceutical responsibility for these preparations.

In 2017, the French-speaking Society for Clinical Nutrition and Metabolism started working on PN standardisation to be applied in France. They propose a limited number of standardised PPN formulations including stability data and storage conditions. Their aim is to decrease risks related to PPN practices in all French hospitals and to harmonise them.

Only few commercialised PN are available for neonatal patients but not used routinely due to patients' varying needs of nutrients and the limited composition flexibility.[15] Standardised PN assures an immediate availability on wards of analysed PN (composition, sterility), minimises the risk of prescribing errors,[17–20] and improves the medical treatment and clinical outcome of the treated inpatients.[3 21]

Our hospital is one of the few hospitals in Switzerland where PPN is prepared individually on wards and at pharmacies. Our neonatology unit is composed of 40 beds, including 18 in the intensive care unit. For the preparation of injectable medication, this unit is equipped with laminar airflow hoods in a non-classified environment, but pharmaceutical aseptic preparation technique is not applied.

In 2014, more than 8500 individual PN and simple dextrose/amino acid mixtures were administered to our neonatal patients (internal project). The majority of these PN were prepared on the ward by nurses, and only 30% were prepared at the pharmacy conforming to current GMP and PIC/S guidelines.

The aim of this study is to evaluate the quality of PN for newborn and preterm infants prepared by nurses on the neonatal ward of a tertiary university hospital. Electrolytes and dextrose concentrations and microbial and endotoxin contamination are analysed in these PN.

METHODS AND MATERIALS

From July 2015 until April 2016, a sample collection of PN prepared by nurses on our neonatal ward was performed. After the PN administration to the patients for a maximum of 24 hours, the residual PN volume was withdrawn from the bag into sterile syringes using aseptic technique (mask, disinfected gloves, hairnet) under a laminar airflow hood located in a non-classified area for drug preparation on the neonatal ward. All bags and withdrawn samples were inspected for visible particles. Tests for invisible particles (e.g.: $CaPO_4$ precipitate) could not be performed due to the small sample volume.

Due to the limited residual volume of PN solution, we decided to focus on the following assays. Two or three of them were performed depending on the available volume.

1. Endotoxin analysis (<1 mL) to prove their absence by means of kinetic colouration of limulus amoebocyte lysate (LAL). The endotoxin limit being 0.5 UE/mL following the European and US Pharmacopoeia, PhEur (2.6.14) and USP <85>.
2. Sterility analysis (2× ~10 mL) in accordance with the PhEur (2.6.1) and USP <71> by incubation of ~10 mL PN solution in two different culture media for 2 weeks. The fluid thioglycolate medium was incubated at 30°C–35°C and the soybean casein digest medium at 20°C–25°C.
3. Chemical analysis (3–5 mL) to determine the quantity of PN components.[22] The concentration of each electrolyte (K^+, Na^+, Ca^{2+}, Mg^{2+}) was measured by means of a capillary electrophoresis (CE) method, and dextrose was quantified by means of an enzymatic method of hexokinase (HK) followed by ultraviolet detection. Due to the amount of analyses necessary to quantify all amino acids, their concentrations were not determined. The obtained results were compared with the medical prescription of the concerned PN.

All collected samples were stored in a fridge for a minimum of time (maximum of 60 hours) before being analysed in order to maintain the contamination status of the withdrawn solution as bacterial growth is limited at 2°C–8°C.

For the endotoxin analysis, we used the Endosafe nexgen-MCS system. Endosafe cartridges containing chromogenic LAL reagent measure colour intensity directly related to the endotoxin concentration in a sample. For economic reasons, equal volumes (<1 mL) of up to three samples were diluted 1:20 with sterile water and vortexed for being analysed once. A positive control furnished by the manufacturer was analysed in parallel to each sample run.

Table 1 Characteristics of capillary electrophoresis

Capillary	BGB (USA), TSP-050375, uncoated fused silica, 64.5 cm, 50 µm ID
Conductivity of buffer	Approximately 20 µA
Temperature of cassette	25°C
Temperature of sample	25°C
Tampon	100 mM Tris-acetate pH 4.5/acetonitrile (80: 20, V/V)
Voltage	30 kV
Injection	40 mbar × 10 s
Duration of analysis	5 min

For the sterility testing, a maximum of 10 mL of the PN sample (≤10% of the medium solution) was injected in each medium solution of 100 mL. The samples were incubated for 2 weeks at 30°C–35°C in the fluid thioglycolate medium and at 20°C–25°C in the soybean casein digest medium. For each sampling a negative control was performed by injecting 10 mL of an intravenous 5% dextrose solution withdrawn aseptically from a new and disinfected vial. After incubation, the solution was inspected for turbidity. The method was validated by imitating a PN preparation of the neonatal ward, mixing the possible components in usual concentrations. This PN solution (10 mL for each test) was inoculated aseptically with a maximum of 100 colony forming units for each of the following species of micro-organisms in accordance with the PhEur (2.6.1) and USP <71>. For the composition analysis approximately 5–10 mL was necessary. Each sample was analysed once. Conforming to the method of Nussbaumer *et al*, the samples were diluted in distilled water to obtain a final concentration between 1 and 4 mM for K^+ and Na^+ and between 0.5 and 2 mM for Ca^{2+} and Mg^{2+}.[22] Addition of 500 µL of LiCl 50 mM as internal standard to the PN solution and dilution ad 20 mL with sterile water for injection. This mixture (500 µL) is analysed by means of a CE, with the characteristics described in table 1. The chloride salts of K^+, Na^+, Ca^{2+} and Mg^{2+} are identified by their retention time (T_r) in the capillary. The results are calculated as follows: ratio=(area cation/T_r cation) / (area Li^+/T_r Li^+).

The quantification of the different cations is done by Excel. A comparator solution is prepared containing all four electrolytes. The determination of dextrose concentration was performed by means of spectrometry using the enzymatic method of HK.[23] An aliquot of each sample calculated from the medically prescribed concentration of dextrose in the PN is diluted ad 100 mL of water for analyses to contain an anhydrous dextrose concentration of 0.5 mg/mL. Of this dilution, 200 µL is mixed with 1.8 mL of HK reagent (e.g.: Gluco-Quant, Roche). The vortexed mixture must react during 4 min before determining the dextrose concentration by using a spectrophotometer (e.g.: Cary 50) at 340 nm. Three other solutions are prepared and analysed for method validation purpose: a furnished standard and an internal laboratory solution at 0.5 mg/mL anhydrous dextrose and a non-coloured solution (water). Each of these solutions is mixed with the HK reagent for a 4 min reaction.

The results of the concentration analyses were expressed in percentages. The mean concentration values and their SD were calculated based on the pooled results of all analyses of each component.

The specifications for PN conformity were justified following the concentration limits of a minimum of 90% and a maximum of 110% for compounded preparations[24] defined by the USP[25] and the Helvetian Pharmacopoeia (PhHelv).[26]

Table 2 Conformity specifications

Component	K^+	Na^+	Ca^{2+}	Mg^{2+}	Dextrose
Pharmacopoeia concentration limits for compounded preparations (%)	90–110	90–110	90–110	90–110	90–110
Internal acceptable concentration limits of pharmacy (%)	85–110	85–115	81–120	81–120	85–120

Internal acceptable concentration ranges have been introduced for the analysed PN components by the pharmacy's laboratory based on the variable influences on the results, like preparation and analysis inaccuracy. The mode of action, potential risk factor and impact of the different components on the clinical outcome of the treated patients were also taken into account. The specifications for PN acceptability were justified following these widened concentration limits. A comparison of the conformity specifications is shown in table 2.

RESULTS

Within 10 months, a total of 127 samples were collected.

Endotoxin testing with a limit of 0.5 UE/mL was performed on all retrieved samples and showed no positive result. All 127 PN prepared by nurses on the neonatal ward were free of endotoxins.

Sterility testing showed no microbial contamination in both media solutions for all 92 analysed PN.

The composition analyses (K^+, Na^+, Ca^{2+}, Mg^{2+}, dextrose) were performed on 110 PN bags, which contained one to five analysed components. Only few PN contained all electrolytes, as the treated patients either were born recently and the blood values were not available yet, or they just needed intravenous hydration to complete the enteral feeding. The quantification of electrolytes represented 118 analyses and dextrose concentration was measured 110 times. None of the analysed PN contained additional or missing prescribed components.

The medical prescription of each component equates to 100% and represents the theoretical value. The measured concentrations are expressed in percentage and represent the real value. The mean real value and the SD of the obtained results were calculated. The number of analyses performed for each component, their concentration range, mean concentration, SD and the median concentration are shown in table 3.

Following the USP and PhHelv concentration limits (90%–110%) for compounded preparations, 48 (21.1%) component analyses representing 37 (33.6%) prepared PN did not conform to their medical prescription, as shown in table 4.

Following the widened concentration limits established by our hospital's pharmacy, 18 (7.9%) component analyses representing 15 (13.6%) of the 110 tested PN were not acceptable for administration from a pharmaceutical point of view. These PN would not have been dispensed by the pharmacy for administration due to the risk of overdose or underdosage.

Table 3 Component analyses and results

Component	Parental nutrition analysed (n)	Range measured (%)	Mean value (%)	±SD (%)	Median value (%)
K^+	34	75–113	97.2	±8.0	97.0
Na^+	14	83–119	99.4	±11.7	97.5
Ca^{2+}	66	58–164	97.5	±13.7	99.0
Mg^{2+}	4	92–102	95.8	±4.5	94.5
Dextrose	110	60–137	96.3	±8.6	97.5

Table 4 Concentration limits and conformity

Component	Pharmacopoeia concentration limits (%)	Preparations out of pharmacopoeia limits, n/n_{tot} (%)	Pharmacy concentration limits (%)	Preparations out of pharmacy limits, n/n_{tot} (%)
K^+	90–110	6/34 (17.6)	85–110	4/34 (11.8)
Na^+	90–110	7/14 (50.0)	85–115	2/14 (14.3)
Ca^{2+}	90–110	20/66 (30.3)	81–120	4/66 (6.1)
Mg^{2+}	90–110	0/4 (0)	81–120	0/4 (0)
Dextrose	90–110	15/110 (13.6)	85–120	8/110 (7.3)

DISCUSSION

The chemical analysis of PN prepared on the neonatal ward by nurses revealed a lack of quality of these preparations for high-risk patients. The quality issue concerned the preparation accuracy, which has a direct impact on the concentration and dosage of the different prescribed PN components. Almost 14% of the 110 tested PN would not have been delivered from the pharmacy to the site for administration because of non-conformity following the widened internal concentration limits. With more than 6000 PN prepared by nurses on the ward in 2014, 14% equate to the administration of more than 840 non-conforming PN bags. Concentrations of the two mostly used components (Ca^{2+}, dextrose) reached from 58% to 164% of the medically prescribed dosage. This confirms the issue of prescription and preparation errors mentioned by Krzyzaniak and Bajorek[17] and Hermanspann *et al*[19]. In comparison, in 2015, only 5 PN out of 2646 prepared at the pharmacy did not pass the chemical analyses of the components and had to be prepared a second time.

Fortunately, the results of the analyses on microbial and endotoxin contamination were negative. No PN contamination was found, which is described as one of the major risks of PN preparations in the publications of Puntis[15] and White[3]. However, as shown by Stucki *et al*,[27] microbial contamination in intravenous medication prepared on wards occurs in around 0.2%. Therefore, our sample size of 92 analysed PN as well as the volume analysed are too small to show contamination. Stucki *et al*'s work confirms the need for a minimum of 500 analyses to detect at least one contaminated preparation. Beneath the 6000 PN prepared by nurses on the ward in 2014, 12 (0.2%) might have been contaminated. To control the cleanroom environment for aseptic preparations, at every working session, the pharmacy performs microbial settle plates and glove prints on culture media plates, which are not done on the ward. In 2015, 14 out of 771 (1.8%) settle plates and 21 out of 1578 (1.3%) glove prints were contaminated. Only with knowledge of non-conformities corrective actions can be undertaken throughout the yearly qualification of each operator by preparing PN with culture media.

As shown in our project, up to 14% of PN prepared on the ward do not conform to their medical prescription and result in an inappropriate treatment of patients. This percentage is probably even more important when analysing all PN preparations realised on the ward. These concentration deviations might be harmful for the patient depending on the component and its mode of action. Concentrations of dextrose, which is the major source of energy and essential for neonatal inpatients, out of the target values may lead to hypoglycaemia or hyperglycaemia and a diminished or exceeded metabolism of amino acids. Calcium is the most abundant electrolyte in human bodies. Most of it

is directly incorporated in skeletal bones. Magnesium is also important for the development of the skeletal bones. In a long term, a deficit of calcium and magnesium may lead to rickets, fractures, bone mineralisation troubles and reduction of growth. Hypokalaemia or hyperkalaemia and hyponatraemia and hypernatraemia may lead to heart rhythm disturbances as potassium and sodium maintain the resting potential of the nerve, muscles and heart cells. A study performed in Western Europe by Bouchoud *et al*[10] in 2007 showed that 12% of PPN are prepared by nurses on the ward without being analysed for composition before administration. This signifies that approximately 2% of all administered PN to paediatric patients may lead to adverse events.

A weakness of our study is the small sample size due to organisational difficulties. Resulting from the relatively high stress level on our neonatal ward, nurses did not always remember to keep the used PN for sampling and hence often discarded them. An alternative to collecting more samples could have been visiting the other, second Swiss hospital where PN is prepared on the neonatal ward, which was a logistical problem due to the necessary sample storage in a fridge before testing.

The recommendations of the American Society of Parenteral and Enteral Nutrition (ASPEN) are already encouraging a standardised process for PN management, but to keep the flexibility to treat patients individually when necessary.[7] These recommendations should be taken as starting point to unify knowledge and experiences to harmonise PN management in hospitals treating newborn and preterm infants. In France, after the death of three neonatal patients in 2014 as a result of contaminated PN, the inspection authority IGAS prohibited all PN preparations by nurses on the hospitals' wards. Additionally, they delegated all responsibility concerning PN preparation exclusively to pharmacists. The approach of the IGAS to centralise PN preparation in hospital pharmacies and to propose national standardised PN formulations is rigid but offers several advantages in quality and organisational questions, and especially increases the security of the patients.

Our project's results suggest two interesting future research projects. One could be a cause identification of the described composition deviations. The reasons for this issue observed in our research were multiple. They included errors in prescription transcription, calculation, dilution, raw material, label preparation and so on. The percentage of these different errors was not evaluated in our study because of a missing traceability of the different steps and the focus on the quality of PN. Another could be an impact evaluation of the administration of non-conforming PN on the treated infants. If performed prospectively, this might cause an ethical problem due to its potential harmfulness to the patients. In our study, the sampling was performed retrospectively and therefore did neither raise ethical concerns nor put patients knowingly at risk.

CONCLUSION

The management of PN preparation for newborn and preterm infants still varies in the entire world, but also within one country.[1 3] The results of this work show that there is a lack of quality of PN preparations when prepared on the ward by nurses. Additionally, these quality issues—component identity and concentration, and microbial and endotoxin contamination—cannot be identified on the ward due to the absence of facilities. Our study emphasises the recommendations published by ASPEN, IGAS and other associations. The preparation of individual PN needs to be centralised at hospital pharmacies where they are produced in cleanrooms in ISO 5 hoods. Standardised PN solutions need to be taken into consideration as they increase quality and security.

The current methods applied on neonatal wards represent major risk factors for the clinical status of patients.[3 4 15] The centralisation and standardisation of PN preparation for newborn and especially preterm infants increase the quality of delivered PN and the security of patients, and reduce errors related to prescription, preparation and administration. These points can only be guaranteed by means of a routinely performed quality control of the PN before administration to vulnerable patients.

What this paper adds

What is already known on this subject

- There is complexity in parenteral nutrition (PN) preparation.
- Neonatal patients are at risk for infections and malnutrition; therefore, the quality of PN preparation is crucial for these patients and has a direct impact on their health status and safety.
- Microbial and chemical quality of PN prepared on wards are not controlled or documented.

What this study adds

- PN prepared on wards by nurses does not conform to their medical prescription.
- On wards, PN is prepared under non-aseptic conditions.

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