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Original article

Safety of parenteral nutrition in newborns: Results from a nationwide prospective cohort study

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SUMMARY

Background & aims: Limited or delayed availability of parenteral nutrition (PN) solutions, as well as difficulties in ordering are often identified as reasons for non-compliance with international guidelines in newborns. This study aims at assessing the modality of use and safety of standardized PN solutions in a nationwide prospective cohort of newborns treated in clinical practice.

Methods: Two premixed fixed formulations with respective osmolarity of 715 and 790 mOsmol/L specifically designed for neonates were made available throughout the country for clinical use from birth onwards. Descriptive data and modality of use were prospectively collected in a case report form, whereas all related and unrelated adverse events were recorded on a separate adverse event form.

Results: A total of 14,167 infants were prospectively included. Mean age was 33 weeks of gestation, and mean weight was 2086 g. The majority of infants (81%) started the parenteral nutrition the first day of life or the day after. The route of parenteral nutrition delivery was peripheral in 47% of the parenteral nutrition periods. During the whole study period, a total of 72 adverse events occurring in 68 infants were reported. Of these adverse events, 59 (0.37% of the nutrition periods), among which 19 serious adverse events, were reported as related to the parenteral nutrition solutions. The events related to parenteral nutrition solutions were general disorders and administration site conditions (n = 42 including 9 cases of cutaneous necrosis), and nutrition and metabolism disorders (n = 17). There was no case of thrombophlebitis. Six of the 19 serious events related to the parenteral nutrition solutions (32%) were due to the misuse of the infusion bag.

Conclusions: These data support the concept that ready-to-use parenteral nutrition formulations can safely provide parenteral nutrition from birth onwards. They further support that parenteral solutions with an osmolarity of 800 mOsm/L are well-tolerated when infused on a peripheral vein. Considering the potential risk of errors and misuses, this study also highlights the need for nutrition practice care guidelines for neonates and for regular campaigns providing information and strategies for a safe use of parenteral nutrition solutions.

1. Introduction

It has become clear that preterm infants require early parenteral nutrition from birth onwards and there is now a considerable body of evidence suggesting that early and enhanced nutrition at this stage may determine various outcomes, including both physical growth and neurological development [1–3]. Current recommendations for preterm infants are to start parenteral nutrition on the first day of life, ideally during the first hours after birth, to avoid interruption of nutrient supply and to steadily increase it to avoid accumulation of nutrient deficits until enteral feeds are established [4,5].

Three types of parenteral nutrition formulations are available: (i) Pharmaceutical industrial formulations with marketing authorization. These products are in line with current standards and meet the needs of a large group of preterm neonates [6,7]. Addition of nutrients is allowed as indicated in the Summary of Product

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Characteristics (SmPC), offering flexibility to these products. (ii) Standardized formulations are also intended to meet the nutritional needs of a large number of premature infants. They are prepared in-house by hospital pharmacists or provided by a pharmaceutical subcontractor in accordance with the Pharmacopeia. (iii) Individualized formulations are in-house compounded by hospital pharmacists or by a private manufacturer, depending on the individual requirements of a neonate. The major drawback of the individualized formulations is the time between the prescription and the parenteral administration that may range between few hours up to 3 days (during weekends for example). It should also be emphasized that sufficient nutritional knowledge is required to adequately prescribe individualized parenteral nutrition.

Advantages of standardized or pharmaceutical industrial formulations include promotion of safer administration, consistent adherence to guidelines, better provision of nutrients, less prescription and administration errors, decreased risk of infection, and cost savings [8,9]. Several studies have demonstrated that standardized formulations are more appropriate in the management of preterm neonates than individualized [10,11].

Surveys conducted in industrialized countries show that nutritional management in neonatal departments are often not in accordance with the existing guidelines [12,13]. The time of parenteral nutrition introduction is often delayed; the initial dosage and the daily rate of progression of macronutrients, particularly proteins and lipids, are frequently lower than those defined by guidelines. Beside the greater need for education and guideline implementation, the limited or delayed availability of individualized parenteral nutrition solutions, as well as difficulties in ordering individualized formulations were often identified as reasons for non-compliance with guidelines [14,15]. In this regard, standardized or pharmaceutical industrial formulations are solutions which allow for the initiation of parenteral nutrition soon after birth.

Considering all the potential risks and disadvantages related to the in-house formulations or the delayed introduction of parenteral nutrition, two premixed fixed formulations were developed, pharmaceutically manufactured and made available for newborns from birth onwards [16]. The objectives of this study were to assess the modality of use and safety of these parenteral nutrition solutions in a large prospective cohort of newborns treated in clinical practice.

2. Material and methods

Two of the five binary parenteral nutritional solutions (Pediaven® AP-HP) specifically developed by the public hospital in Paris, France (Assistance Publique-Hôpitaux de Paris; AP-HP) for use in children when enteral nutrition is not possible, insufficient or contraindicated, were specifically made to be used in newborns from birth onwards.

These solutions were granted a “temporary authorization for use” in April 2007 allowing prospective collection of modality of use and safety data before the market authorization which was granted by the French authorities in 2011. The owner of the authorization was the AP-HP, and preparations were manufactured and supplied by FRESENIUS KABI France. The parenteral solutions were made available to all neonatal units throughout France for routine clinical use during the temporary authorization for use which lasted almost 4.5 years from 30 April 2007 to 15 October 2011.

The composition of the solutions is reported in Table 1. Pediaven® AP-HP NOUVEAU-NE 1 (NN1) was indicated to meet the daily requirements of nitrogen (amino acids of the L series), glucose, electrolytes, trace elements and fluid requirements of neonates during the first 24–48 h of life, whether they are born preterm or not, and Pediaven® AP-HP NOUVEAU-NE 2 (NN2) was indicated to meet the daily requirements of nitrogen (amino acids of the L), glucose, electrolytes, trace elements and fluid requirements of neonates, born preterm or not, from the second day of life onwards. These solutions were at first presented as one-chamber bags, then as two-chamber bags containing an amino acid and a carbohydrate solution in separate chambers that need to be mixed together shortly before administration. The type and amount of amino-acids, vitamins, water, sodium chloride, calcium, and phosphate that can be safely added to the solutions was tested prior to the study initiation and the information was provided to the physicians. The choice of binary over tertiary solutions was determined during the development phase. The “Y-site” addition of lipids was chosen so the volume and type of lipids administered could be individually adjusted to the patient's needs and the lipid administration could be temporarily stopped if required. The osmolarity of the solution were 715 mOsmol/L and 790 mOsmol/L, respectively, allowing for both central and peripheral venous use.

Table 1
Composition of the parenteral nutrition solutions Pediaven® AP-HP NOUVEAU-NE 1 and Pediaven® AP-HP NOUVEAU-NE 2.

Composition per liter (l)	Pediaven® NN1	Pediaven® NN2
Glucose (g/l)	100	100
Amino acid (g/l)	15	17
Total nitrogen (g)	2,14	2,44
Non-protein energy (kcal)	400	400
Total energy (kcal)	460	470
Sodium (mmol/l)	4.5	20
Potassium (mmol/l)	0	17
Calcium (mmol/l)	9.4	7.6
Magnesium (mmol/l)	2.1	1.6
Chloride (mmol/l)	5	26
Phosphorus (mmol/l)	0	9.1
Lactate (mmol/l)	4	3
Gluconate (mmol/l)	19	15
Chrome (μg/l)	2	3
Copper (μg/l)	230	260
Fluor (μg/l)	80	90
Iodine (μg/l)	10	10
Manganese (μg/l)	6	6
Zinc (μg/l)	2030	2300
Osmolarity (mOsm/L)	715	790

The use of these solutions was monitored using a protocol of therapeutic use. The protocol included a Summary of Product Characteristics, an information note to parents, adverse event form, and follow-up case report form. The follow-up case report form did not collect efficacy data; only descriptive data about the patient (demographics), the condition, the parenteral nutrition, treatment duration, lipid and vitamin supply, and other supplements, and potential comments on nutrition solution tolerance, were collected. One follow-up case report form was filled for each parenteral nutrition period; therefore, one patient could have several follow-up forms.

The causality assessment for adverse events to the parenteral solutions was performed by means of the compulsory approach implemented in France; which is the “French Drug Reaction Assessment Method” as described by Begaud et al. [17]. Briefly, this method combines 3 chronological criteria and 3 semiological criteria, accompanied with a bibliographic scale for differentiating expected and unexpected adverse drug reactions.

The data collection was approved by the CNIL (National Commission on Informatics and Liberty). The submission of progress reports to the French National Authority for Health (ANSM) about the Pediaven® use was performed semiannually, as it is mandatory according to the French regulations.

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