Clinical Nutrition 32 (2013) 331–337

Contents lists available at SciVerse ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Efficacy and safety of a parenteral amino acid solution containing alanyl-glutamine versus standard solution in infants: A first-in-man randomized double-blind trial

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ARTICLE INFO

Article history:
Received 27 September 2011
Accepted 13 September 2012

Keywords:
Parenteral nutrition
Amino acids
Infants

SUMMARY

Background & aims: Efforts are directed at reaching the optimal composition of pediatric amino acids (AA) infusions. The goal was to demonstrate the safety and efficacy of a newly developed parenteral AA solution containing alanyl-glutamine (GLN-AA) compared to Standard-AA.
Methods: This is a randomized (2:1), double-blind, multicentre clinical pilot trial. Infants after surgical interventions were allocated to receive GLN-AA or Standard-AA over a minimum of 5 days to maximum of 10 days. AA profiles in blood samples obtained at baseline, day 7, and end of treatment were compared to normal ranges. Data regarding safety, and efficacy were also collected.
Results: Infants were comparable for (safety population) gestational age at birth (36 vs 38 weeks), birth weight (2460 vs 2955 g), and day of life during start intervention (1 vs 2 days). Plasma AA profiles in infants treated with GLN-AA ($n = 13$) were closer the normal ranges than those in infants treated with Standard-AA ($n = 6$). There were no clinical or statistical differences in adverse events, safety and efficacy parameters between both groups.
Conclusion: This first-in-man study shows that GLN-AA is safe in infants after surgical interventions, and is well tolerated. Compared to reference values, GLN-AA better reflects the amino acid requirements of the infant.

1. Introduction

The newborn infant is in a critical stage of development, and adequate nutrition is necessary to promote growth and optimal neurological development.[1] Healthy newborn infants have a higher metabolic rate and energy requirement per unit body weight than older infants and children. Post-surgical infants may even need more energy than healthy newborns, including higher amounts of amino acids (AA).[2–4] Recovery after surgery will possibly be delayed and normal growth will on hold when the composition of AA infusions is not ideal. There are standard AA solutions which are not optimally designed for term and preterm infants. In standard AA solutions, certain AAs are too low, too high or missing when fed to preterm or term infants.[5–7]

The numerous studies on addition of different AA such as glutamine or cysteine have brought conflicting results, and further trials have been advocated.[8–10] A new AA solution (GLN-AA, Fresenius Kabi, Bad Homburg, Germany) was designed exclusively for children of all ages (from premature neonates to infants) to better suit the need for children who require AA for a prolonged period of time for example after gastrointestinal surgery in the neonatal period. Fresenius decided under feasibility criteria to adjust the following components. It contains alanyl-glutamine as a precursor for glutamine in order to provide adequate amounts of glutamine, glycyl-tyrosine as a precursor for tyrosine, and acetyl-cysteine as a source of cysteine. Additionally arginine and taurine are increased compared to the reference solution (Standard-AA). GLN-AA was designed to better suit the AA requirements of parenterally fed infants and children.

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http://dx.doi.org/10.1016/j.clnu.2012.09.001

In this report we describe a first-in-man study to demonstrate the safety and efficacy of GLN-AA compared to Standard-AA, as reflected by plasma AA concentrations in infants requiring parenteral nutrition after surgical interventions due to major congenital gastrointestinal malformations.

2. Material and methods

2.1. Study design

This pilot phase II study was an international, multi-center, randomized controlled, double-blind trial to compare the amino acid and safety profiles in infants treated with GLN-AA or Standard-AA for 5–10 days. Four pediatric surgical services in tertiary referral hospitals participated (Erasmus MC – Sophia, Rotterdam, The Netherlands; Klinik für Kinder- und Jugendmedizin, Mannheim, Germany; VU University Medical Center, Amsterdam, The Netherlands; Cliniques Universitaires Saint-Luc, Brussels, Belgium).

The inclusion criteria were the following: gestational age ≥34 weeks and age ≤23 months; birth weight for newborns ≥1840 g or within ±2 SD for standard weight at inclusion for infants other than newborns (these are based on the reference values applicable in Caucasian newborns derived from Nelson Textbook of Pediatrics,[11]); surgical intervention of the gastrointestinal tract due to congenital malformations, an estimated need for parenteral nutrition of at least 5 days, and parental informed consent. The following exclusion criteria were applied: enteral nutrition ≥25% of total energy intake per day, considerable impairment of renal function, inborn congenital malformation other than of the bowel, severe congenital heart disease, major chromosomal abnormalities, inborn metabolic disorders and severe liver dysfunction. The study protocol was approved by all institutional review boards (Erasmus MC Rotterdam, the Netherlands; VU University Medical Center Amsterdam, The Netherlands; Klinik für Kinder- und Jugendmedizin Mannheim, Germany; Cliniques Universitaires Saint-Luc Brussels, Belgium).

2.2. Randomization and blinding

Patients were randomized to treatment using the method of randomly permuted blocks. The ratio of patients allocated to GLN-AA versus Standard-AA was 2:1. The next eligible patient for randomization received the lowest available randomization number at the study site. All investigators, physicians and nurses involved in the care of included patients were blinded to the allocation of treatment, as well as the parents.

2.3. Study products

GLN-AA (Fresenius Kabi, Bad Homburg, Germany) was the investigational solution; this 10% pediatric AA solution was administered isonitrogenously compared to the control solution (Vaminolact®, Fresenius Kabi, Bad Homburg, Germany; in this paper named Standard-AA), a 6.5% pediatric AA solution containing 18 AA, and taurine. Standard-AA is predominantly used for the supply of AA as part of pediatric parenteral nutrition. GLN-AA is a new solution, and compared with Standard-AA contains the 2 dipeptides glycyl-tyrosine as precursor for tyrosine, and alanyl-glutamine as precursor glutamine, and it contains acetyl-cysteine. Furthermore, the concentrations of taurine and arginine are higher than those in Standard-AA, whereas phenylalanine is lower compensated by a higher amount of tyrosine GLN-AA does not contain glutamic acid and aspartic acid. The parenteral nutrition regimens were based on the requirements of the ESPGHAN Guidelines as published in 2005.[12]

Treatment was started the day after surgery, and lasted for a minimum of 5 days and a maximum of 10 days. Dosage of both study products was increased stepwise over the first 3 days, from 1.0 g/kg/day at day 1–2.0 g/kg/day at day 2and 2.5 g/kg/day at day 3 (with a range of ±0.5 g/kg/day). The latter dosage was then maintained until the end of study. The intention was infuse the study medication for at least 24 h, with a minimum of 20 h per day. Treatment was stopped prematurely when enteral nutrition exceeded ≥25% of total energy intake. If parenteral nutrition with AA needed to be continued after 10 days, patients in both groups were given Standard-AA as long as clinically indicated.

2.4. Study endpoints

The primary study endpoint was the profile of all AA in plasma after last treatment, and comparison between both study groups. Secondary endpoints were safety and efficacy (growth outcome) parameters. Safety parameters are liver enzymes, blood gas values (pH, BE), blood glucose levels, incidence of sepsis, and adverse events including local tolerance of infusion. For all these values there was a predetermined list with cut-off values above which the study had to be stopped. Moreover a Data Safety Monitoring Board was appointed to regularly check these parameters. An adverse event was defined as any untoward medical occurrence in a patient which did not necessarily have a causal relationship with the treatment An adverse event could therefore be any unfavourable and unintended sign (i.e. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. As pharmacokinetic variables plasma concentrations of the dipeptides (Ala–Gln and Gly–Tyr), and N-Acetyl-Cysteine (NAC) were defined. Efficacy parameters included body weight, head circumference, and pre-albumin levels.

2.5. Data collection and monitoring

All patient data were recorded in case report forms. Clinical parameters such as weight, blood glucose, study solution, concomitant medication, concomitant nutrition and (serious) adverse events were documented each study day. Local tolerance of the infusion site was scaled when the study solution was infused peripherally. Blood samples were drawn during steady state infusions conditions (except at baseline) at three time points (baseline, end of study day 7 and at day 10). These samples were drawn together with blood samples taken for routine care from with an intravenous puncture. Last follow-up visit was 28 days (±7 days) after end of last infusion.

2.6. Analytical method

Free AA (all standard AA except cysteine, and the non-standard (non-canonic) AA taurine, citrulline and ornithine) and dipeptide (Ala–Gln, Gly–Tyr) concentrations in plasma samples were quantified by a triple-quadruple mass spectrometer after separation of matrix components by high-performance liquid chromatography on a cyano column (LC-MS/MS system consisted of a 1100 series binary pump (Agilent) and a Sciex API4000 (Applied Biosystems) mass spectrometer with turbo ion spray). Proteins were precipitated by sulphosalicylic acid. Thiols (including cysteine and N-Acetyl-L-Cysteine) of the plasma samples were reduced with dithiothreitol (methods for amino acid analysis according to Medizinisches Labor, Bremen, Germany).