FOOD-CT-2005-007036

EARNEST

EARly Nutrition programming- long term follow up of Efficacy and Safety Trials and integrated epidemiological, genetic, animal, consumer and economic research

Instrument: Integrated Project

Thematic Priority 5.4.3.1: Food Quality and Safety

Final public report on activity 6.2.2

Title of activity: A prospective, randomized, double-blind crossover study comparing rhBSSL (recombinant human Bile Salt Stimulated Lipase) and placebo added to infant formula during one week of treatment in preterm infants born before 32 weeks of gestational age

Period covered from 15.04.2005 to 14.10.2010

Start date of project: 15.04.2005 Duration: 5,5 Years

Organisation Name of Lead Contractor for this report: Biovitrum AB

Introduction:

The superiority of human milk as a nutritional source for term as well as preterm infants has been manifested in many studies and expert group recommendations. In addition to containing important nutrients, the fat composition of human milk provides energy and important building block fat molecules that are critical for infant development. The recommended feeding method world-wide is breastfeeding. However, as breastfeeding is not always possible or recommended for medical reasons, infant formula or banked and non-banked pasteurized breast milk is used. Both are, however, in some respects nutritionally suboptimal for newborn infants.

Pancreas and liver functions are not fully developed at birth, and in premature infants this is particularly notable. Breast-fed infants digest and absorb fat (and importantly long-chain polyunsaturated fatty acids) more efficiently than formula-fed infants (i, ii). In addition to infant formulas of similar fat composition, mother's milk also contains a broad-specificity lipase, BSSL that promotes highly efficient fat absorption from human milk. The human lactating mammary gland synthesizes and secretes BSSL that, after specific activation by primary bile salts, contributes to the breastfed infant's endogenous capacity for intestinal fat digestion (iii, iv, v, vi).

BSSL has a broad specificity against different lipids and hydrolyses triglycerides, phospholipids, vitamin esters and cholesterol esters. Due to risks of viral infection and to a lesser degree transmission of pathogenic bacteria, donor milk used in so-called milk banks is generally pasteurized before it is used. This procedure inactivates some of the milk's ingredients, including BSSL, and thereby compromises fat absorption. The addition of recombinant human BSSL (rhBSSL) to pasteurized breast milk or to formula is expected to enhance the use of the energy supply in the milk/formula resulting in improved growth and maturation of the infant.

In order to study the clinical effects of rhBSSL the following study was performed:

5 study centers in Italy recruited preterm infants to the study: The study centers were:

- *Polytechnic University of Marche and Salesi Children's Hospital, University of Ancona, Ancona, Italy (Principal Investigator: Professor Carnielli)*
- *Policlinico 'Agostino Gemelli' Catholic University of the Sacred Heart, Rome, Italy*
- *Azienda Ospedaliera di Padova-Dipartimento di Pediatria Padua, Italy*
- *U.O. Neonatologia, Patologia Neonatale e Terapia Intensiva – Azienda Universitaria Policlinico Umberto Rome, Italy*
- *Azienda Ospedaliera "Ospedale Policlinico Consorziale"-U.O. Neonatologia e Terapia Intensiva Neonatale Bari, Italy*

Overall study design:

In this Phase II double-blind crossover study, patients were randomized to receive infant formula supplemented with rhBSSL at a concentration of 0.15 g/L, or infant formula with placebo for the first 7 days. After a washout period of 2 days, the patients crossed over to the other treatment regimen during a second 7-day treatment period. Collection of feces for assessment of the fat absorption was performed during the last 3 days of each treatment period. Patients were enrolled and randomized into the study at the neonatal intensive care unit after fulfilling the inclusion and exclusion criteria. To ensure that all patients received a comparable treatment regimen at baseline, infants receiving another formula prior to study entry were switched to the study formula (produced by Ordesa) at enrollment. The infant formula chosen for use in this study has been developed to replicate, as closely as possible, the fat content and composition found in mother's milk.

Objectives of the clinical study

The objectives of the study were to compare the absorption of total fat and of selected fatty acids, as well as growth and safety in preterm infants treated with 0.15 g/L rhBSSL or placebo. After the protocol was approved by ethics committees the first preterm infant was enrolled into the study on March 26, 2008. 33 infants with a mean gestational age of 32.6 weeks were randomised to receive one-week treatment with rhBSSL and placebo. 32 infants completed the study.

It took 12,5 months to recruit all 33 preterm infants which was according to plan.

After all data had been collected and analysed the following results were reported: weight improved with 3.7 g/kg/day in the rhBSSL group compared to the placebo group.The difference was statistically significant. No difference in tolerability between rhBSSL and placebo was seen. A manuscript is being prepared and all data from the clinical study will be published in a scientific paper.

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[i] Bernbäck S, Bläckberg L, and Hernell O. The complete digestion of human milk triacylglycerol in vitro requires gastric lipase, pancreatic colipase-dependent lipase, and bile salt-stimulated lipase. Clin Invest. 1990 April; 85(4): 1221–1226.

[ii] Carnielli V P, Verlato G, Pederzini F, Luijendijk I, Boerlage A, Pedrotti D, and Sauer P J. Intestinal absorption of long-chain polyunsaturated fatty acids in preterm infants fed breast milk or formula. Am J Clin Nutr, 1998 67, 97–103.

[iii] Gordon, H. H., and H. McNamara. 1941. Fat excretion of preterm infants. I. Effect on fecal fat of decreasing fat intake. Am. J. Dis. Child. 62:328-337.

[iv] Fomon, S. J., E. F. Ziegler, L. N. Thomas, R. L. Jensen, and L. J.Filer, Jr. 1970. Excretion of fat by normal full-term infants fed various milks and formulas. Am. J. Clin. Nutr. 23:1299-1313.

[v] Atkinson, S. A., M. H. Bryan, and G. H. Andersson. 1981. Human milk feeding in premature infants: protein, fat and carbohydrate balances in the first two weeks of life. J. Pediatr. 99:617-624.

[vi] Chappell, J. E., M. T. Clandinin, C. Kearney-Volpe, B. Reichman, and P. W. Swyer. 1986. Fatty acid balance studies in premature infants fed human milk or formula: effect of calcium supplementation. J. Pediatr. 108:439-447.