

INFANT NUTRITIONAL FORMULA WITH RIBO-NUCLEOTIDES

FIELD OF THE INVENTION

The invention relates to an improved enteral nutritional formula and more particularly to infant formulas which contain ribo-nucleotide equivalents at a level of at least 10 mg/100 Kcal of formula and wherein the ribo-nucleotide components are at specific ratios.

BACKGROUND OF THE INVENTION

The composition of human milk serves as a valuable reference for improving infant formula. However, human milk contains living cells, hormones, active enzymes, immunoglobulins and components with unique molecular structures that cannot be replicated in infant formula. Unlike human milk, infant formula must remain stable on the shelf for up to thirty-six (36) months. These fundamental differences between human milk and infant formula often mandate differences in the composition to achieve similar clinical outcome.

Human milk has served as a valuable reference for improving infant formula. The investigation of human milk components has stimulated many investigations into what constituents may be added to infant formula. Greater knowledge of the composition of human milk affords the opportunity to design infant formulas that are closer to that of human milk. However, it becomes increasingly apparent that infant formula can never duplicate human milk. Many constituents in human milk are bioactive and because of synergies among these components there is little reason to believe that the same compound would have the same bioactivity in infant formula. The likelihood of this possibility is further diminished when the impact of heat treatment for sterilization and long-term storage of the formula is considered. The present invention is based, in part, on the concept of providing a formula which matches the performance of breast milk in most parameters without attempting to actually duplicate the delicate balance of human milk components.

The composition of human milk differs appreciably from that of other species and much attention has been paid to the various components. Several investigators have reported on the nucleotide content of milk from humans [Janas, L. M. et al: *The Nucleotide Profile of Human Milk*. *Pediatr. Res.* 16:659-662(1982) and Gil, A et al: *Acid-soluble Nucleotides of Human Milk at Different Stages of Lactation*. *Journal of Dairy Research* (1982), 49, 301-307.] The numerous publications cited in the Janas and Gil references also relate to the nucleotide composition of human milk and, in combination, leave one skilled in the art with a confused and conflicting understanding of the nucleotide composition of human milk. None of the prior art discloses the minimum level of nucleotide equivalents taught by the present invention nor the ratio of the four elements (adenosine, cytidine, guanosine and uridine) to each other. Most importantly the prior art does not suggest or disclose a formula that is superior to human milk in enhancing the immune response of a human.

Nucleosides are nucleotides minus the one to three phosphate groups. Nucleosides are a class of chemical compounds that are of importance in physiological and medical research. They may be obtained from the partial decomposition (hydrolysis) of nucleic acids. Nucleosides contain a

purine or pyrimidine base linked to either d-ribose, forming ribosides, or d-deoxyribose, forming deoxyribosides. Nucleosides are nucleotides minus the phosphorus group. Representative of the nucleosides are adenosine, cytidine, guanosine, inosine and uridine.

Nucleotides (nucleosides plus at least one phosphate group) are the fundamental units of nucleic acids. The nucleotides found in nucleic acids are phosphate esters of the nucleosides. The term nucleotides is also sometimes applied to compounds not found in nucleic acids and which contain substances other than the usual purines and pyrimidines. The nucleotides inosine-5'-monophosphate and guanosine-5'-monophosphate are used as flavor potentiators.

Nucleotides are ubiquitous, low molecular weight compounds that participate in energy metabolism and modulation of enzymatic reactions. In addition, nucleotides are components of compounds that are crucial in the synthesis and catabolism of carbohydrates, lipids, protein, and nucleic acids. Clearly nucleotides and their metabolites are important determinants of numerous cellular processes.

Adequate cellular supplies of nucleotides in humans and animals are maintained by two pathways; the salvage pathway and de novo synthesis. The salvage pathway involves recovery of nucleotides and nucleosides liberated from metabolism (such as catabolized nucleic acids). De novo synthesis of nucleotides requires the precursors aspartate, glutamine, glycine, and carbamoyl phosphate. The salvage pathway generally supplies sufficient quantities of nucleotides even in tissue with rapidly proliferating cells, including enterocytes, erythrocytes and immune cells. It is also known that addition of nucleotides to the diet inhibits the de novo pathway and activates the salvage pathway in the liver and extrahepatic tissue, especially in enterocytes.

Dietary sources rich in nucleotides include meats, fish, legumes, and dairy products. Nucleotides are primarily present in polymeric forms (DNA, RNA and nucleoproteins) in these foods and are degraded by ribonucleases, deoxyribonucleases and proteases, yielding nucleotides. Subsequent action of phosphatases yields nucleosides which appear to be the preferred form for absorption. Some additional digestion to free purine and pyrimidine bases may occur. Studies have been published that indicate that a specific transport system(s) exists for the absorption of nucleosides and bases.

Most dietary nucleotides are degraded, excreted, or utilized before reaching the systemic circulation. Although dietary nucleotides appear to have little access to the systemic circulation, they have been implicated as having numerous systemic effects. Reports indicate that dietary nucleotides influence the response to sepsis, alter blood lipid profiles, enhance brain function, and increase iron absorption, gut mucosal growth, and gut bifidobacteria populations.

U.S. Pat. No. 3,231,385 discloses and claims an active phosphatase free cow's milk which contains at least two of the respective disodium salts of (a) cytidine 5'-monophosphate in the amount of 10 to 20 mg/L of cow's milk, (b) guanosine 5' monophosphate in the amount of 0.2 to 0.4 mg/L of cow's milk, (c) uridine 5'-monophosphate in the amount of 1.2 to 1.4 mg/L of cow's milk, (d) guanosine 5'-diphosphate in the amount of 0.4 to 0.6 mg/L of cow's milk, (e) uridine 5'-diphosphate glucose in the amount of 0.5 to 1.0 mg/L of cow's milk, (f) uridine 5'-diphosphate galactose in the amount of 0.5 to 1.0 mg/L of cow's milk and (g) uridine 5'-diphosphate glucuronic acid in the amount of 1.0 to 3.0 mg/L of cow's milk.

U.S. Pat. No. 4,994,442 discloses and claims the addition of nucleosides and/or nucleotides to infant formula to pro-