

Clinical Article

Tolerance and Safety of Energy-Dense Enteral Formulae for Young Children

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Abstract

The safety and tolerance of energy-dense enteral pediatric formulae were evaluated and compared with a standard formula. Children aged 1-6 years requiring tube feedings to provide $\geq 75\%$ of their daily estimated energy needs for 21 days were evaluated in this phase III, randomized, open-label, multicenter study. Subjects received a control formula, Pediasure® (C; 1.0 kcal/mL) or an experimental formula similar in nutrient composition but higher in caloric density (1.5 kcal/mL) with or without fiber (EF and E, respectively). Subjects (n=94) returned for 3 weekly visits. Gastrointestinal parameters improved ($p < 0.05$) in all groups. Energy intake was comparable among groups, but was achieved with lower ($p < 0.0001$) volumes in E and EF relative to C. Weight gain was greater ($p < 0.01$) in E versus C. Adverse event reporting was similar among groups. Energy dense formulae are an option for children with fluid restrictions or increased energy or fiber needs without compromising safety or tolerance. *Int Pediatr.* 2003;18(2):95-99.

Key words: fructooligosaccharides, energy-dense, gastrointestinal tolerance, fiber, enteral nutrition, child nutrition

Introduction

Nutritional management is crucial for proper growth and development in the pediatric patient. Children with illness may have lower than normal appetites, resulting in reduced caloric intake and

creating a challenge for nutritional management. Children who are unable to maintain an adequate energy and nutrient intake may require modifications in their feeding habits, during which time oral nutritional supplementation may be indicated and effective.¹ Children who are unable to swallow or meet their energy needs orally may require tube feeding.

Enteral nutrition offers several advantages over parenteral nutrition, including reduced costs, fewer complications and the preservation of gut mucosal integrity which limits bacterial translocation.²⁻⁴ Pediatric enteral formulae have been designed for oral or enteral use to provide complete, balanced nutrition for children.

The nutritional needs of sick children can be quite variable. In some cases, fluid intake must be limited. Energy dense formulae with and without fiber offer increased calories in a decreased volume and may be of benefit for children who have special needs. The target population for this type of formula includes subjects with the following needs or conditions: high caloric requirements; weight loss or malnutrition; disease-related growth faltering; neurological conditions; and other medical conditions resulting in increased caloric needs and/or fluid restrictions.

Formulae with fiber may help reduce gastrointestinal complications such as diarrhea or constipation, common problems which have been associated with enteral feeding.

The source of fiber in the experimental formula (EF) used in this study includes oat fiber, soy fiber (soy polysaccharide), gum arabic and carboxymethylcellulose and meets the ratio recommended by the Federation of American Societies for Experimental Biology (75% insoluble and 25% soluble fiber).⁵ This blend of fiber sources represents the types of fiber found in a solid diet containing a wide variety of foods and was selected for its water absorbing ability, fermentability, contribution to stool bulking and minimal contribution to formula viscosity.⁵⁻⁹

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Data from animal and clinical studies have shown that this blend of soluble and insoluble fibers, when added to enteral formulae, can help to normalize bowel functioning.

Formula EF also includes fructooligosaccharides (FOS). FOS are soluble fibers that are found naturally in many foods, including onions, bananas, peaches, wheat, barley, garlic and Jerusalem artichokes. FOS is a preferred substrate for probiotic bacteria such as *Bifidobacteria* and *Lactobacilli* species. FOS enhances the growth and metabolic activity of these acid-forming bacteria, consequently lowering the pH of the gastrointestinal tract and inhibiting the growth of pathogenic bacteria in the gut.

The primary objective of this study was to determine and compare the safety and gastrointestinal tolerance of two energy dense enteral formulae (E and EF) with a standard enteral formula (C) in children aged 1-6 who require tube feeding for at least 21 days. Secondary objectives included the examination of the efficacy of the energy dense formulae based on changes in body weight, gastrointestinal symptoms and energy intake.

Methods

This phase III multicenter, randomized controlled, open label comparative study was conducted in 15 sites located in Canada, Italy, Spain, and the United Kingdom. The study was approved by the local research ethics committees of each country and was conducted in accordance with Good Clinical Practices as described in the Guideline for Good Clinical Practice, the Declaration of Helsinki, and Abbott Laboratories Standard Operating Procedures. Written informed consent was obtained from each child's parent or legal guardian prior to enrollment.

Children between the ages of 1-6 years who required at least 75% of their daily tube feed from the study formulae were considered eligible for participation in the study. Subjects had to maintain this level of consumption for at least 14 days. Subjects were excluded from the study if: (1) the subject was intolerant or allergic to any ingredient in the study products; (2) the subject had impaired glucose metabolism; (3) the subject was unavailable for the required follow-up visits; (4) the subject required parenteral nutrition or less than 75% of energy needs from tube feeding; (5) the subject participated in another study and did not

have permission from the study monitor to participate in this study; (6) contra-indications to enteral feeding were present; (7) cisapride was taken; (8) the subject suffered from uncorrected Hirschsprung's disease or pelvic floor dysynergy; (9) the subject was acutely impacted or constipated; (10) the subject had protracted diarrhea.

Subjects were randomized to receive one of three study products: (1) C: a control formula, Pediasure®; (2) E: Pediasure® Plus; or (3) EF: Pediasure® Plus with fiber (Abbott Laboratories, Zwolle, Netherlands). The macronutrient composition of these milk-based formulae was (% of energy) 11.2% protein, 44.6% carbohydrate, and 44.8% fat. The formula with fiber contains a patented blend of 75% insoluble and 25% soluble fibers. The fiber sources were oat fiber, soy fiber (soy polysaccharide), gum arabic and carboxymethylcellulose. The total non-starch polysaccharide content of EF is 0.75 g/100ml. The product also contains 0.35 g/100ml fructooligosaccharides (FOS).

Subjects were fed by enteral tube for 21 days. They were assessed on study days 7, 14, and 21. The gastrointestinal symptoms evaluated did include: nausea, vomiting, diarrhea, constipation, abdominal distention, burping and flatulence. Each of the seven symptoms was recorded daily by the subject's caregiver on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Total GI scores were calculated based on the sum of these events. Investigators prescribed additional water as needed on a case by case basis.

Energy intake, weight, frequency and consistency of stool output, and adverse event reporting were also recorded. Stool frequency was recorded using a 5-point scale (1 = watery; 2 = loose; 3 = soft; 4 = formed; and 5 = hard).

Statistics

Continuous demographic and baseline variables were summarized by descriptive statistics. Mean change in total GI symptom score and stool frequency and consistency between baseline and each assessment period were compared between treatment groups using a repeated measures analysis of variance. Compliance and change in anthropometric measurements were compared between treatment groups using analysis of variance.

Results

Subject population

A total of 94 out of the 113 enrolled (83%) subjects completed the study per protocol; groups were similar in terms of age and initial weight. Compliance days were also similar. Subject characteristics and compliance days are presented in Table 1.

Gastrointestinal Tolerance

From baseline to day 21, total GI tolerance scores decreased significantly ($p < 0.05$) in each group (Fig 1). No significant differences were detected among treatment groups.

Stool frequency/consistency

Stool frequency among the three groups was not statistically different in the change from baseline to Day 21 ($p = 0.64$) (Fig 2). There were also no statistically significant differences among groups in stool consistency changes from baseline to Day 21 ($p = 0.17$) (Fig 2).

Weight/Height

Differences in change in height among the three groups were not statistically significant. There was a statistically significant ($p = 0.005$) difference among groups for weight gain. Mean weight gain in group E (0.52 ± 0.5 kg) was significantly ($p = 0.0013$) greater than weight gain in group C (0.18 ± 0.4 kg) (Fig 3).

Formula Energy and Volume Consumption

Energy intake from the three formulae was comparable among the three groups. Volume intake was

significantly ($p < 0.05$) lower with E and EF relative to C (Fig 4), as would be expected with calorically denser formulae.

Adverse events

The incidence of adverse events was not significantly different among groups. The most common adverse events, pyrexia, nasopharyngitis and cough, were not related to treatment. Most treatment-emergent adverse events occurred in the GI system and included vomiting, nausea, eructation, flatulence, diarrhea, abdominal distention, retching, and constipation. Differences in the distribution of these adverse events among groups were not statistically significant.

Discussion

Nutritional formulae play an important role in the dietary management of children who have fluid or volume restrictions or specialized energy and/or fiber needs that cannot be met with standard enteral formulae. This study evaluated the safety and tolerance of energy-dense formulae with or without fiber in comparison to a standard pediatric formula. Based on the results from this study, these energy dense formulae increased daily energy intake, improved gastrointestinal symptoms, and were as safe and as well tolerated as the standard formula (C) by children ages 1-6 years. Changes in gastrointestinal parameters also suggest that adding fiber and FOS to the energy dense enteral formulae provides additional benefits.

When patients are being treated by enteral feedings, a routine assessment of gastrointestinal, metabolic, mechanical, and growth parameters is essential.

Table 1 - Summary of Demographic Variables and Compliance Days

	C	E	EF	p-value
	n = 37	n = 40	n = 35	
Age (yrs)	2.5 ± 1.68	2.9 ± 1.72	3.0 ± 1.95	0.41
Sex	19 M; 18 F	26 M; 14 F	14 M; 21 F	0.10
Height (cm)	87.6 ± 12.0	91.5 ± 12.9	90.4 ± 13.2	0.41
Weight (kg)	13.0 ± 4.2	12.9 ± 3.6	13.6 ± 3.8	0.72
Compliance (days)	19.3 ± 2.2	19.3 ± 1.8	19.5 ± 2.0	0.89

C = Control formula, Pediasure®; E = Pediasure® Plus; EF = Pediasure® Plus with Fiber. Values are presented as mean ± SD. No statistically significant differences among groups occurred for age, sex, height, weight, or compliance days.

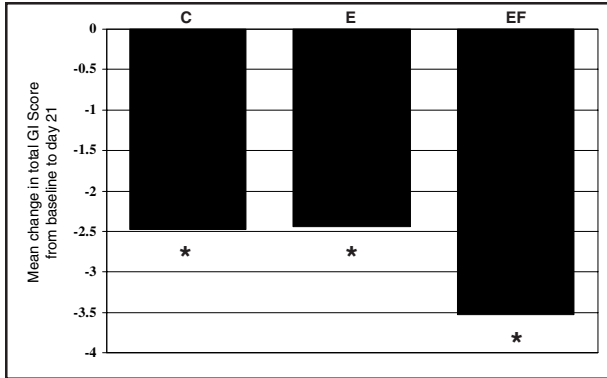


Fig 1 - Changes in Total Gastrointestinal (GI) Score from Baseline to day 21. C = Control formula, Pediasure®; E = Pediasure® Plus; EF = Pediasure® Plus with Fiber. Values represent mean changes in GI scores from baseline to day 21. GI symptoms evaluated did include: nausea, vomiting, diarrhea, constipation, abdominal distention, burping and flatulence. Each of the seven symptoms was recorded daily by the subject's caregiver on a four-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Total GI scores were calculated based on the sum of these events. *Scores were significantly ($p < 0.05$) lower than baseline.

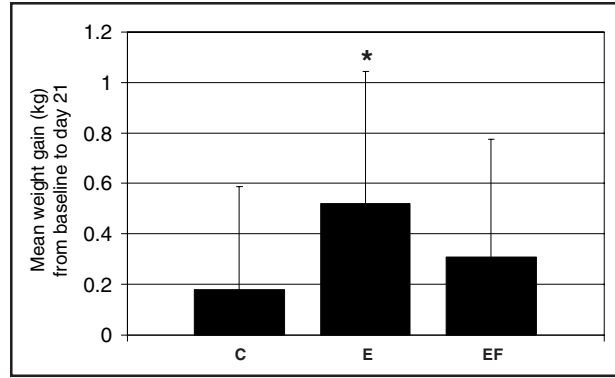


Fig 3 - Weight Gain. C = Control formula, Pediasure®; E = Pediasure® Plus; EF = Pediasure® Plus with Fiber. Values represent mean weight gain \pm SD. *Mean weight gain in group E was significantly ($p < 0.05$) greater than mean weight gain in group C.

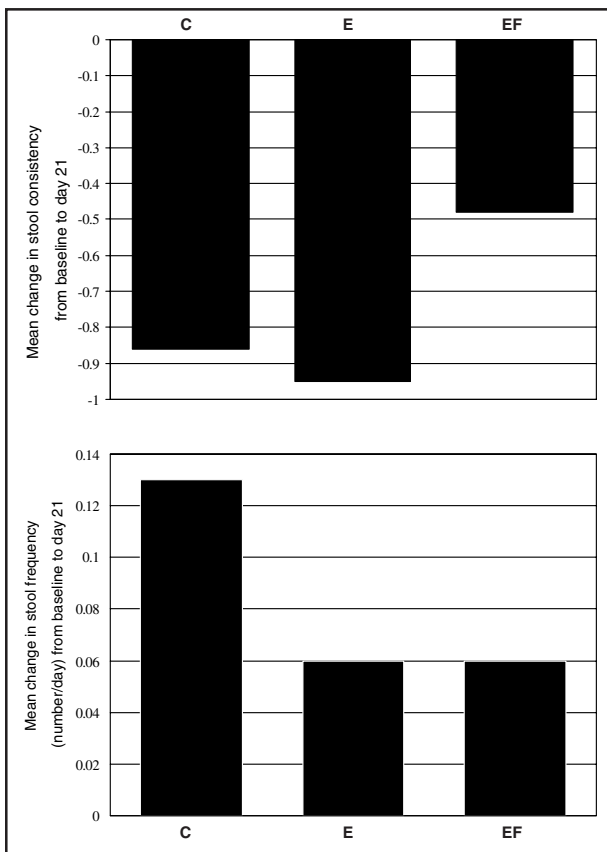


Fig 2 - Changes in Stool Characteristics from Baseline to day 21. C = Control formula, Pediasure®; E = Pediasure® Plus; EF = Pediasure® Plus with Fiber. Values represent mean scores. A 5-point scale (1 = watery; 2 = loose; 3 = soft; 4 = formed; and 5 = hard) was used to evaluate stool consistency. Changes in stool consistency or frequency were not significantly different among groups.

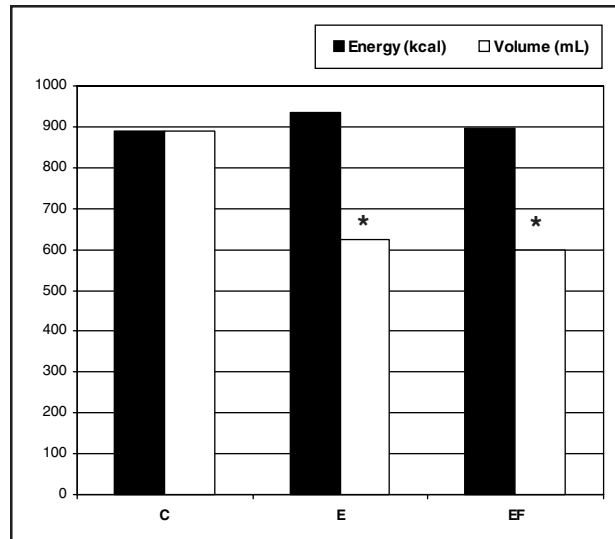


Fig 4 - Formula Energy and Volume Consumption. C = Control formula, Pediasure®; E = Pediasure® Plus; EF = Pediasure® Plus with Fiber. Values represent mean energy (kcal) and volume (mL) intakes. *Volume intake in groups E and EF are significantly ($p < 0.05$) lower than volume intake in group C.

Tolerance of enteral feedings can be assessed by noting the presence or absence of gastrointestinal problems such as vomiting, abdominal distention, and diarrhea.¹⁰

In this study, nutritional supplementation with all three formulas improved GI parameters over the course of the study. Based on the reduction in total GI tolerance scores, the subjects had fewer incidences of diarrhea, constipation, burping, defecation, flatulence, nausea and vomiting over the course of nutritional supplementation. This may be due to the composition of the formulas. They do not contain lactose. Furthermore, all of them contain MCT oil,

which is easier to digest by children who are ill. The greatest reductions in GI symptoms were observed with the formula containing fiber and FOS. Improvements in total GI scores with supplementation were observed without any significant changes in stool consistency or frequency. However, it was evident that children receiving the EF formula passed more formed stools as compared to the children in the other groups. This is probably due to the bulking capacity of this fiber blend.

All of the children gained weight in this study. Children receiving the energy dense formulae with or without fiber had greater weight gains than did the control group. Such increases in weight might be attributed to the increased energy intake, which was achieved in all groups. However, in both experimental groups – E and EF, this was achieved with less volume. For children who have fluid and/or volume restrictions, this is of special importance.

These increases in energy intake, weight, and improvements in GI symptoms were achieved with minimal adverse events. A wide range of treatment-related events occurred at low incidence in all groups. There were no statistically significant differences among groups in terms of adverse event reports.

In this study, the energy dense formulae, with or without fiber, were received in a similar manner in comparison to the standard formula in terms of: treatment compliance; percentage of formula consumed; and changes in height, stool frequency and stool consistency over a 21-day feeding period. Additionally, subjects gained greater amounts of weight when receiving an energy-dense formula with or without fiber. Based on adverse event reporting and gastrointestinal tolerance scores, energy dense formulae

with or without fiber are as safe and tolerable as a standard pediatric enteral feed. This study has shown that energy dense formulae with or without fiber can be used safely in children with fluid or volume restrictions or increased energy or fiber needs.

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