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An Antiregurgitation Milk Formula in the Management of Infants with Mild to Moderate Gastroesophageal Reflux

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ABSTRACT

Background: Thickened milk formulas are used to treat infants with gastroesophageal reflux (GER), but these substances often increase the duration of reflux episodes and worsen symptoms, and they have been associated with diarrhea, constipation, and cough.

Objectives: The aims of this study were to determine the efficacy of an antiregurgitation milk formula in the clinical and laboratory setting in infants with proved GER, to investigate any possible adverse events (cough and change in the number of bowel movements or the consistency of stools), and to identify its effects on height and body weight.

Methods: Infants with recurrent vomiting and GER who were not responsive to standard treatment were eligible for the study. Infants in the treatment group (group A) were managed for 4 weeks with a specific antiregurgitation milk formula (with cornstarch and an increased amount of casein), and those in the control group (group B) were given a standard milk formula. The number of episodes of vomiting, regurgitation, and cough, as well as the frequency and consistency of stool, height, and body weight were noted at least 10 days before and during the study. A second pH monitoring was performed after 4 weeks in both groups.

Results: Fifty-six infants (30 boys, 26 girls; mean [SD] age, 3.1 [1.2] months) were included in the study; 30.4% had mild GER; 44.6%, moderate GER; and 25.0%, severe GER. Significantly more infants in group A than in group B (50.0% vs 14.3%, respectively) with mild or moderate GER had normal findings on the second pH monitoring ($P < 0.05$). Changes in the reflux index and in the mean number of vomiting and regurgitation episodes were significantly different between the 2 groups ($P < 0.05$). No significant differences in changes in the mean number of bowel movements and cough events or in the consumption time of the 2 formulas were found between the 2 groups.

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Conclusion: Infants with mild or moderate GER can be managed effectively with this antiregurgitation milk formula. Improved clinical and laboratory findings were seen in the majority of infants, and the formula was well tolerated, without adverse events. (*Curr Ther Res Clin Exp.* 2003;64:270–278) Copyright © 2003 Excerpta Medica, Inc.

Key words: gastroesophageal reflux, infants, antiregurgitation milk formula.

INTRODUCTION

The management of gastroesophageal reflux (GER) includes nonmedical measures, such as head-elevated prone positioning, nutritional modifications, and drug treatment.[1] For >4 decades, thickening of milk formulas with substances such as carob flour and rice was a common therapeutic measure[2]; however, the results of these studies for the treatment of GER were often contradictory. These substances, despite their benefits, often increase the duration of reflux episodes and worsen symptoms,[3,4] and they have been associated with diarrhea, constipation, and cough.[5–7]

Newer, thickened milk formulas have become available. In one of these formulas, cornstarch has been substituted for some of the lactose, and the total amount of casein has been increased. This formula is considered to have better viscosity without negatively affecting gastric emptying. The increased amount of casein regulates stomach pH, and casein precipitates do not cause reflux, as is the case with whey.[8,9]

The aims of this study were to determine the efficacy of this antiregurgitation milk formula in the clinical and laboratory setting in infants with proved GER, to investigate any possible adverse events (cough and change in the number of bowel movements or the consistency of stools), and to identify its effects on height and body weight.

PATIENTS AND METHODS

The definitions of the terms used in this single-center, placebo-controlled, nonrandomized, open-label study appear in Table I.[10] During a 4-year period

Table I. Definitions of the terms used in this study.[10]

Term	Definition
Regurgitation (or "spitting up")	The passive return of gastric contents into the esophagus and mouth
Vomiting (or emesis)	The gastric contents that are expelled from the mouth
Gastroesophageal reflux (GER)	A functional or physiologic process in a healthy infant with no underlying systemic abnormalities

(January 1999 to October 2002), full-term infants with recurrent vomiting were assessed for inclusion in the study. Infants were eligible for the study if they had vomiting and/or regurgitation for ≥2 weeks and had not responded to standard treatment (eg, positioning, nutritional modifications) during that period.

Based on clinical history, physical examination, and laboratory investigation, infants whose recurrent vomiting and regurgitation was caused by or thought to be caused by disease (eg, bovine milk allergy, pyloric stenosis, metabolic disorders, gastrointestinal dysplasias, central nervous system disorders, urinary tract infections) were excluded from the study. They were also excluded if they had ever received drug therapy for GER.

To be included in the study, infants had to be born at term and be apparently healthy, without clinical symptoms or laboratory findings suggestive of complications of GER (eg, hematemesis, iron deficiency anemia, growth retardation, bronchopulmonary events).

For at least 10 days before pH measurement and daily during the study, parents were instructed to complete a form each day indicating the number of episodes of vomiting, regurgitation, and cough, as well as the frequency and consistency of stools. Height and body weight also were recorded before and during the study to determine whether the infants' caloric intake of the antiregurgitation milk formula was equivalent to that of normal milk formulas, because the formula contained an increased amount of casein (casein:albumin ratio changed from 30:70 to 80:20), and 26% of the lactose was replaced with precooked cornstarch.

All infants underwent 24-hour esophageal pH monitoring using a 2-channel pH meter (Synectics Medical AB, Stockholm, Sweden). The recording equipment (Digitrapper Mk III, Synectics Medical AB) carries 2 electrodes—the reference electrode, which is attached to the skin, and the pH-recording electrode, which ends in 2 antimony sensors 5 cm apart. Thus, the pH is recorded at 2 sites in the esophagus. The pH measuring and recording electrode was inserted into the esophagus through the nasal tract, and the length of the nose–lower esophageal sphincter (L) was calculated as[11–13]:

$$L\ (cm) = (0.252 \times \text{height}\ [cm] + 5) \times 0.87$$

Electrode position was confirmed radiographically. Before monitoring, the electrode was calibrated in special buffers. During the 24-hour monitoring period, no changes were made in the infants' usual activities (eg, meals, sleep, play, rest). According to the manufacturer's requirements and international data,[11–13] esophageal pH values were recorded every 6 seconds. Reflux episodes were defined as episodes in which esophageal pH remained ≤4.0 for >15 seconds.[14–16] (A pH value ≥8.0 was considered as alkaline.[17]) Results were analyzed on a PC system using the manufacturer's software (Synectics Medical AB). The endoscopic method in this study was used previously in our laboratory.

The reflux index (RI) is the percentage of the total time during pH monitoring that esophageal pH is ≤4.0. GER was classified as mild (RI values occurred 5% to 10% of monitoring time), moderate (>10% to 20%), and severe (>20%).[12,16] The criteria used to diagnose GER appear in Table II.[18–21]

Once the presence of GER was established, infants were divided into 2 groups as follows: the first infant diagnosed in each reflux-severity group was placed in the treatment group (group A), and the second infant in that severity group was placed in the control group (group B). This pattern was repeated until every infant in the study had been assigned to a treatment group. Data were collected and analyzed for all children at the end of the study. Infants of group A received an antiregurgitation milk formula for 4 weeks. The formula contained an increased amount of casein (casein:albumin ratio, 80:20), and 26% of the lactose was replaced with precooked cornstarch. The children of group B continued to receive a normal milk formula (the same for all). The approximate contents of the antiregurgitation and the standard milk formulas, respectively, were as follows: calories, 68 and 67 kcal/100 mL; carbohydrate, 7.2 and 7.2 g/100 mL; fat, 3.7 and 3.6 g/mL; and protein, 1.6 and 1.5 g/mL.

Parents were advised to continue the nonmedical instructions for feeding and positioning they had been following prior to the study. At the same time, clinical manifestations (eg, the number of vomiting, regurgitation, and cough events; number and consistency of stools), milk tolerance, and duration of feedings were recorded daily by the parents on a specific form.

According to the indications for pediatric esophageal pH monitoring of the North American Society for Pediatric Gastroenterology and Nutrition,[19] a second pH monitoring was considered useful, because it could lead to clinically important changes in diagnosis, treatment, or prognosis. The second pH monitoring was performed after 4 weeks in both groups of infants, and the results were correlated with those recorded before the study.

The study was approved by the institutional review board of the Hippocration Hospital (Thessaloniki, Greece). Before the study, all parents provided written informed consent.

Table II. Gastroesophageal reflux (GER) diagnosis criteria* during 24-hour esophageal pH measurement.[18–21]

1. Reflux index = the percentage of total time that esophageal pH is ≤4.0 (normal values ≤5% of total recording time on 24-h esophageal monitoring)
2. Number of reflux episodes lasting >5 min (abnormal when >7 episodes/d)
3. Acid clearance = the percentage of the total duration of time (in min) of GER episodes with pH <4.0 to the number of GER episodes (abnormal when >4 min)
4. Longest reflux episode (abnormal when >20 min)

*The criteria refer to measurements >16 h. At least 2 of these criteria should be abnormal for a diagnosis of GER to be made.

Statistical Analysis

Calculations and statistical analyses were made using GraphPad InStat (GraphPad Software, Inc., San Diego, California). Data are presented using descriptive statistics. Because of the small sample size, the Fisher exact test was used for incidence comparisons between groups. The nonparametric Wilcoxon test was performed for paired comparisons of continuous variables. $P < 0.05$ was considered statistically significant.

RESULTS

One hundred two full-term infants (53 girls, 49 boys) aged 37 days to 4 months with recurrent vomiting of >2 weeks' duration were assessed for inclusion in the study. GER was established in 56 of the 102 infants (54.9%) (30 boys, 26 girls; mean [SD] age, 3.1 [1.2] months). Of these, reflux was classified as mild in 17 (30.4%), moderate in 25 (44.6%), and severe in 14 (25.0%). Group A comprised 28 infants (8, 13, and 7 with mild, moderate, and severe reflux, respectively). Group B comprised 28 infants (9, 12, and 7 with mild, moderate, and severe reflux, respectively) (Table III). At the second pH monitoring, 14 (50.0%) in group A compared with 4 (14.3%) in group B had normal findings ($P < 0.05$). Between baseline and the end of week 4 in the infants who received the antiregurgitation milk formula, RI had improved significantly (14.6 [6.5%] vs 7.5 [6.6%], respectively; $P < 0.001$). Two of the symptoms of GER—mean number of episodes of vomiting per day (4.7 [2.5%] vs 1.5 [1.7%], respectively; $P < 0.001$) and mean number of episodes of regurgitation per day (6.0 [4.5%] vs 2.7 [2.9%], respectively; $P < 0.001$)—also decreased significantly in group A (Table IV). Furthermore, these changes were statistically significant ($P < 0.05$) compared with the changes in group B. Between baseline and the end of week 4, neither RI (14.7 [6.4%] vs 13.4 [7.3%], respectively) nor any of the symptoms of GER decreased significantly in group B.

Table III. Gastroesophageal reflux (GER) severity (no. [%] of patients) in the 2 groups before and after treatment.

	GER Severity Before Treatment					
	Mild		Moderate		Severe	
GER Severity After Treatment	Group A (n = 8)	Group B (n = 9)	Group A (n = 13)	Group B (n = 12)	Group A (n = 7)	Group B (n = 7)
Normal	7 (87.5)*	3 (33.3)	7 (53.8)*	1 (8.3)	–	–
Mild	1 (12.5)*	6 (66.6)	4 (30.8)†	5 (41.7)†	–	–
Moderate	–	–	2 (15.4)†	6 (50.0)†	5 (71.4)	1 (14.3)
Severe	–	–	–	–	2 (28.6)	6 (85.7)

*$P < 0.05$ versus group B.
†$P = 0.03$ versus before treatment.

Table IV. Mean (SD) reflux index and frequency of vomiting, regurgitation, bowel movements, and cough events before and 4 weeks after the administration of an antiregurgitation milk formula (group A) and in controls (group B).

	Before Treatment		After Treatment	
	Group A	Group B	Group A	Group B
Reflux index	14.6 (6.5)	14.7 (6.4)	7.5 (6.6)*	13.4 (7.3)
Vomiting episodes per day	4.7 (2.5)	3.0 (1.2)	1.5 (1.7)*	2.7 (1.4)
Regurgitation episodes per day	6.0 (4.5)	4.9 (2.5)	2.7 (2.9)*	4.2 (2.1)
Bowel movements per day	2.6 (0.8)	3.3 (2.1)	2.6 (0.8)	3.1 (2.0)
Cough episodes per day	0.4 (0.7)	0.4 (0.7)	0.3 (0.5)	0.3 (0.5)

*$P < 0.001$ versus before treatment and $P < 0.05$ versus group B.

At the end of the study (week 4), no significant difference was found in either height or body weight of the infants in the 2 groups. Furthermore, the mean number of bowel movements and cough events did not change significantly in the infants who received the antiregurgitation milk formula.

The mean (SD) consumption time of the antiregurgitation milk formula did not differ significantly from that of the normal milk formula (16.1 [5.2] minutes vs 17.0 [4.8] minutes). The antiregurgitation milk formula was well tolerated by all of the infants in the 2 treatment groups.

DISCUSSION

According to various studies, rice flour as a milk-thickening agent is hydrolyzed more quickly than other milk-thickening agents in the stomach and its effectiveness is decreased. The time of gastric emptying also is delayed, which may cause constipation.[2,22] Infants taking milk with rice as a milk-thickening agent have been reported to experience more cough events.[7] Carob bean gum as a milk-thickening agent also has been associated with some problems; fermentation products are created in the large intestine, causing an increase in abdominal pain, colic, and diarrhea. Finally, low-fat, high-carbohydrate milk formulas do not improve RI, as determined by 24-hour esophageal pH monitoring.[23]

In a study of 30 infants with GER, Vandenplas and Sacre[6] used carob bean gum as a thickening agent in milk formulas and performed a second 24-hour esophageal pH monitoring after 7 to 14 days. They found that only 20% of the infants showed clinical and laboratory improvement (RI, <5%). The rest of the infants showed clinical improvement and decreased number of reflux episodes ($P < 0.001$), but RI and the number of reflux episodes lasting >5 minutes were identical. Moreover, the duration of the longest reflux episode increased significantly ($P < 0.001$). In our study, 50.0% of infants who received the special antiregurgitation-milk formula had normal results of second pH monitoring. Specifically, 87.5% of the infants with mild GER and 53.8% of those with moderate

GER had normal second pH measurements. Moreover, 30.8% of infants with moderate GER showed improvement in the degree of reflux. No infant with severe GER had normal results on the second pH measurement; however, some improvement (from severe to moderate) was found in the severity of reflux.

The greater improvement found in our study (50.0%) compared with the improvement found by Vandenplas and Sacre[6] (20%) could be attributed to the fact that the latter used carob bean gum as a thickening agent instead of the cornstarch plus an increased amount of casein that we used in our study. Moreover, they did not correlate reflux severity with therapeutic response, which we found to be inversely correlated (patients with mild or moderate GER showed a higher response rate [87.5% and 53.8%, respectively]).

Clinical improvement of infants with GER who were fed milk thickened with agents such as carob bean gum or dry rice cereal has been reported in various studies.[3,6] Orenstein et al[3] found that vomiting and regurgitation were dramatically reduced when dry rice cereal was used as a thickening agent in milk formulas (33% and 87%, respectively). The same conclusion was reached by Vandenplas and Sacre,[6] who administered carob bean gum as a milk-thickening agent. These findings are in agreement with our results, where regurgitation and vomiting were decreased significantly ($P < 0.001$).

Increased cough events, which were noted in other studies[3,7] using rice cereal as a milk-thickening agent, were not recorded in our study. Moreover, milk tolerance was excellent in all infants. The use of thickening agents in milk formulas sometimes causes changes in the stool consistency or frequency. In particular, rice cereal causes constipation and carob bean gum causes diarrhea.[23] We did not notice any change in stool consistency or frequency with the antiregurgitation milk formula.

CONCLUSIONS

Based on the results of this study, the use of a milk formula thickened with cornstarch and having an increased amount of casein (80:20) is indicated for the treatment of mild to moderate uncomplicated GER. In our study, the majority of infants with this condition showed clinical and laboratory improvement. Furthermore, this formula does not seem to increase cough events and has no effect on stool consistency or frequency. Finally, the tolerance of the milk and its effect on height and body weight are similar to those of normal milk formulas. Medical intervention is required only in severe GER or when complications appear.

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