Digestive
and
Liver Disease
Formerly Published as the Italian Journal of Gastroenterology and Hepatology

Cornstarch thickened formula reduces oesophageal acid exposure time in infants

I. Xinias[a], N. Mouane[b], B. Le Luyer[c], K. Spiroglou[a], V. Demertzidou[a], B. Hauser[d], Y. Vandenplas[d,*]

Amsterdam • Boston • Jena • London • New York • Oxford • Paris • Philadelphia • San Diego • St. Louis

doi:10.1016/S1590-8658(04)00496-7

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Digestive and Liver Disease 37 (2005) 23–27
Digestive and Liver Disease
www.elsevier.com/locate/dld

Alimentary Tract

Cornstarch thickened formula reduces oesophageal acid exposure time in infants

I. Xinias[a], N. Mouane[b], B. Le Luyer[c], K. Spiroglou[a], V. Demertzidou[a], B. Hauser[d], Y. Vandenplas[d,*]

[a] *Third Department of Paediatrics, Hippocration Hospital, Konstantinoupoleos 49, GR 546 42 Thessaloniki, Greece*
[b] *Paediatric Gastroenterology, Hôpital pour Enfants, Rabbat, Morocco*
[c] *Department of Paediatrics, Groupe Hospitalier du Havre, Le Havre, France*
[d] *Paediatric Gastroenterology, Academisch Ziekenhuis Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium*

Received 27 May 2004; accepted 28 July 2004
Available online 27 October 2004

Abstract

Background. Infant regurgitation is a phenomenon causing worldwide parental distress and anxiety. Parental reassurance and dietary advices regarding feeding techniques and volumes are helpful in the management. Guidelines also recommend the use of thickened formula. However, the impact of thickened feeding on the frequency of acid reflux is still a matter of debate. Therefore, we evaluated the effect of a casein predominant formula thickened with a specifically selected and treated cornstarch on the frequency and duration of acid reflux episodes.

Methods. Ninety-six formula-fed infants with a mean age of 93 days, presenting with episodes of regurgitation and vomiting occurring more than five times a day and with an abnormal oesophageal pH monitoring, were randomised to a regular infant formula ($n=45$) or cornstarch thickened casein predominant formula ($n=51$) for 28 days. A second pH monitoring was performed at the end of the study period (26 ± 5 days). Symptoms were daily recorded in a diary by the parents for 28 days.

Results. At inclusion, the pH-metric parameters did not differ between the control and the intervention group. Results of pH monitoring at baseline and at the end of the study did not differ in the control group on the regular infant formula. However, in the group with the casein dominant cornstarch thickened formula, all pH-metric parameters (reflux index (% of the investigation time with a pH < 4.0), number of reflux episodes >5 min, duration of the longest reflux episode) decreased significantly. The frequency of vomiting and regurgitation did not differ between both groups at baseline, remained unchanged in the control group, but decreased significantly in the intervention group.

Conclusion. A casein dominant formula thickened with a specifically treated cornstarch reduces oesophageal acid exposure, and reduces the frequency of clinical symptoms.

Keywords: Cornstarch; Gastro-oesophageal reflux; Infant; Oesophageal pH monitoring; Reflux; Regurgitation; Starch; Thickened formula

1. Introduction

Gastro-oesophageal reflux (GOR) is defined as the involuntary passage of gastric contents into the oesophagus. Virtually all infants experience some degree of GOR with symptoms ranging from a simple burp to persistent vomiting [1]. The frequency of regurgitation peaks at 3 months of age and usually resolves by 6–12 months [2]. Worldwide, about 20% of parents seek medical help because of the episodes of regurgitation [2]. Thickening of the feeds has been since many years the standard treatment approach for infantile regurgitation [3]. However, parental reassurance alone was also suggested to reduce episodes of regurgitation as shown in the first placebo-controlled trial [3]. Thickening agents such as rice cereals (popular in USA) and bean gum starch (popular in Europe) are frequently added to infant formula [4]. Thickened infant formula with cornstarch and potatostarch,

* Corresponding author. Tel.: +32 2 477 57 80; fax: +32 2 477 57 83.
E-mail address: yvan.vandenplas@az.vub.ac.be (Y. Vandenplas).

1590-8658/$30 © 2004 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.dld.2004.07.015

rice and bean gum has been developed and commercialised [5–7].

Although not all GOR is acid, acid GOR is likely to be the target since acid exposure is related to symptoms such as discomfort, irritability, pain and oesophagitis. Although infant irritability is not only caused by oesophageal acid reflux [8], exposure of the oesophageal mucosa to acid reflux remains a major pathophysiological mechanism of GOR-disease. Monitoring oesophageal pH is considered to be the gold standard to quantify the frequency and duration of acid reflux episodes. The technique is safe and results are reproducible [9].

The aim of this prospective, randomised intervention study was to evaluate the efficacy of an infant formula thickened with a specifically treated cornstarch versus standard infant formula to reduce oesophageal acid exposure time in exclusively formula-fed infants with regurgitation.

2. Patients and methods

Study patients ($n=96$) were recruited in four centres: Thessaloniki (Greece), Rabbat (Morocco), Le Havre (France) and Brussels (Belgium). Participation to a double blind, prospective, randomised (with sealed envelopes) trial was proposed to the parents of infants who were presented because of troublesome regurgitation and/or vomiting. Although the formulae were blinded, it is obvious that parents were able to observe that the thickened formula had a higher viscosity, although the cornstarch thickened formula has the particularity to be only slightly more viscous when ingested, and to thicken mainly in the stomach. At inclusion, all infants were exclusively formula-fed, and had not been treated before. All infants were 'healthy', except for the excessive regurgitation and/or vomiting. If infants were very irritable, had haematemesis, passed black stools, had chronic cough, had episodes of cyanosis, or had any other medical problem, they were excluded. As a consequence, all infants were on a regular starter formula. A dietetic formula (hydrolysate, soy, ...) was considered as a therapeutic intervention meaning that the infant was not healthy except for the regurgitation or vomiting, and thus not eligible for inclusion.

The composition of both test formulae, presented to the parents in identical presentation, is listed in Table 1. The formula change was the only therapeutic intervention. The caloric content of both formulae was identical. The thickened formula is casein predominant and contains a moderate amount of medium chain triglycerides. The starch is specially treated re-gelatinised cornstarch.

At baseline, frequency of regurgitation (effortless passage of refluxed gastric contents into the oral pharynx and the mouth with effortless drooling out of the mouth), vomiting (forceful expulsion of the refluxed gastric contents from the mouth) and number of stools were recorded in a diary. Parents recorded regurgitation, vomiting and defecation in a diary during the whole intervention period. The data presented concern the diary data of the 3 days before inclusion and the last 3 days of the intervention period. Data on volume intake were not recorded (since it was estimated that ingested volumes would be biased by the volume that was regurgitated).

Table 1
Composition of normal and thickened infant formula (per 100 ml)

	Standard infant formula	Thickened formula
Energy (kcal)	65	64.5
Protein (g)	1.6	1.7
Casein/whey (%)	50/50	80/20
Lipid (g)	3.3	3.1
MCT (%)	18.6	19.4
Carbohydrates (g)	7.2	7.4
Lactose (%)	70	75
Maltodextrins (%)	30	
Starch (%)		25

The first pH monitoring was performed at baseline and had to be abnormal to be eligible for inclusion (reflux index (% of the investigation time with a pH < 4.0) >5%); the second pH monitoring was performed after 26 ± 5 days. The hardware and software used for pH monitoring were identical in the four centres. Methodology of oesophageal pH monitoring was according to ESPGHAN recommendations [10]. The formula intake during the pH monitorings was standardised at a range of 130–160 ml/(kg day) and divided over four to six feedings. The following parameters were analysed: reflux index, the number of reflux episodes per hour, the number of reflux episodes lasting more than 5 min, the duration of the longest reflux episode.

The statistical significance of difference was tested by either a two-tailed unpaired t-test or Wilcoxon singed rank test, whichever was appropriate. p-values of less than 0.05 were regarded as significant. The protocol was submitted to and approved by the ethical committee of the Hippocration Hospital; all parents signed an informed consent.

3. Results

At inclusion, antropometric data between both groups did not differ (Table 2). The mean age of the 96 infants at inclusion was 93 ± 35 days. Weight gain during the intervention (mean 26 ± 5 days) was 746 ± 246 g in the group receiving the cornstarch thickened formula in comparison to 642 ± 229 g in the group on regular infant formula, or daily weight gain in the cornstarch thickened group was 28.5 ± 12.1 and 24.3 ± 8.1 g/day in the regular infant formula group. The difference in daily weight gain between both groups is 17.3%, but just did not reach statistical significance ($p=0.06$).

Results of oesophageal pH monitoring at inclusion were abnormal in all children and did not differ between both groups (Table 2). The second pH monitoring was performed

Table 2
Patient characteristics at baseline and after 4 weeks

	Regular formula	Thickened formula	p
Number of infants	45	51	
Age			
Baseline (days)	94 ± 32	92 ± 35	
Weight (g)			
Baseline	4803 ± 707	4905 ± 836	0.54
4 weeks	5411 ± 638	5649 ± 707	0.10
Gain/4 weeks	642 ± 229	746 ± 246	0.08
Gain/day	24.3 ± 8.1	28.5 ± 12.1	0.06
Episodes of regurgitation/day			
Baseline	4.77 ± 2.35	5.60 ± 4.15	0.69
After 4 weeks	4.31 ± 2.01	2.57 ± 2.71	0.0001
p	0.36	<0.0001	
Episodes of vomiting/day			
Baseline	3.09 ± 1.24	4.34 ± 2.42	0.04
After 4 weeks	2.74 ± 1.37	1.45 ± 1.65	0.0011
p	0.39	<0.0001	
No. of stools/day			
Baseline	3.80 ± 2.34	2.62 ± 0.77	0.05
After 4 weeks	3.54 ± 2.03	2.60 ± 0.81	0.08
p	0.78	0.82	

after a mean duration of intervention of 26 (±5 days). None of the patients dropped out. No side effects due to the intervention were recorded. After all pH studies had been performed, the code was broken, and the pH-monitoring results at the end of the study were analysed. In the control group, all four pH-metric parameters at baseline and at the end of the study were extremely comparable (differences NS) (Table 3). But in the intervention group, all four pH-metric parameters had decreased significantly (all $p < 0.001$).

Table 3
pH-monitoring results at baseline and after 4 weeks

	Baseline	4 weeks	p
Reflux index			
Regular formula ($n = 45$)	13.3 ± 6.4	11.4 ± 7.0	0.18
Thickened formula ($n = 51$)	14.9 ± 10.2	6.8 ± 6.2	<0.001
p	0.30	<0.01	
No. reflux ep/h			
Regular formula ($n = 45$)	10.6 ± 5.8	8.7 ± 4.9	0.09
Thickened formula ($n = 51$)	11.5 ± 13.3	6.2 ± 10.2	<0.001
p	0.60	0.14	
No. R ep > 5 min			
Regular formula ($n = 45$)	6.1 ± 3.7	5.4 ± 4.2	0.38
Thickened formula ($n = 51$)	7.0 ± 4.5	2.9 ± 3.4	<0.0001
p	0.27	0.03	
Long R Ep			
Regular formula ($n = 45$)	23.8 ± 14.0	19.3 ± 10.5	0.09
Thickened formula ($n = 51$)	30.8 ± 34.8	10.8 ± 8.9	<0.001
p	0.20	<0.001	

No. reflux ep/h: number of reflux episodes per hour; No. R ep > 5 min: number of reflux episodes lasting more than 5 min; Long R Ep: duration longest reflux episode (in minutes).

4. Discussion

The study population consisted of infants presenting with excessive regurgitation and/or vomiting and the percentage of oesophageal exposure time had to be more than 5% [11]. However, infants did not present with symptoms suggesting GOR-disease. Infant regurgitation in formula-fed infants is a frequent cause of parental concern. According to literature published till now, thickening of formula feeding has been demonstrated to reduce almost consistently the frequency and volume of regurgitation [3,4,12–15]. However, again according to published literature, the impact of thickened formula on acid reflux is at borderline or absent [3,12]. Recently, Wenzl et al. [12] suggested a non-significant decrease in non-acid reflux, without any difference in oesophageal height reached by the remaining reflux episodes. Thus, there is a discrepancy between the clinical observation (decrease in regurgitation) and the results of investigation techniques such as pH-metry and impedancemetry (no change in acid and non-acid reflux).

Because of this clinical efficacy, thickened formula has become very popular. Also regarding cornstarch, when used as a thickening agent, this clinical efficacy has been well established previously [13,16]. This raised concern that dietary treatment which alleviates symptoms such as regurgitation and/or vomiting but without decreasing acid exposure to the oesophageal mucosa may be inappropriate for subjects with oesophagitis or severe GOR-disease. But, Ramirez-Mayans et al. [13] reported previously that a formula that was prethickened with re-gelatinised cornstarch did not only result in a significant reduction of episodes of regurgitation and vomiting, but also reduced significantly acid reflux: the number of acid reflux episodes, the duration of the longest reflux and the reflux index (% of the investigation time with a pH < 4.0) decreased significantly. The design of the study by Ramirez-Mayans was comparable to the design of the study discussed here: 'healthy' infants, except for excessive regurgitation and vomiting were randomised to a formula thickened with rice cereal or a formula thickened with cornstarch. The rice cereal thickened formula decreased regurgitation but not vomiting, whereas cornstarch thickened formula reduced regurgitation and vomiting. Bean gum has been shown to be more effective than rice cereal [17]. Rice cereal did not decrease oesophageal acid exposure since oesophageal pH-monitoring parameters at baseline and at the end of the study (after 1 month) had not changed. However, pH-monitoring parameters had significantly decreased in the cornstarch thickened formula group [13].

The benefit of thickened infant formula has to be considered against the risk for side effects, as was suggested by the Nutritional Committee of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition [18]. Bean gum, which is used in some thickened formulae, may occasionally cause malabsorption of micronutrients and may cause abdominal distension and discomfort since the colonic flora ferments bean gum [19]. Good nutrition is essential for normal growth and development of infants. The significant

decrease of regurgitation, vomiting and acid reflux resulted in a better weight gain in the group with the cornstarch formula in comparison to the standard formula. This nutritional benefit outweighs eventual side effects as hypothetically suggested by the ESPGHAN Nutritional Committee [18].

Cornstarch is an appropriate carbohydrate to add to formula as a thickening agent for several reasons. Children less than 6 months of age can easily digest cornstarch [20]. Since in comparison to bean gum, cornstarch provides additional calories, the amount of the other nutrients providing calories in the formula was adapted in order to maintain an equal caloric content in both formulae. Cornstarch does not interfere with the absorption of other nutrients, such as may be the case for micronutrients with bean gum thickened formula [20]. Casein forms a milk curd, which delays gastric emptying, and may result in a reduction of reflux [21]. Commercialised bean gum casein predominant thickened formula results in a reduction of regurgitation and vomiting, but no decrease in the number of long lasting reflux episodes [3]. Cornstarch causes an intragastric dispersion of the casein curd, resulting in a normalisation of gastric emptying [22]. The addition of medium chain triglycerides also accelerates gastric emptying [23,24]. However, it remains unclear why cornstarch thickened formula reduces oesophageal acid exposure. Speculatively, it can be hypothesised that because of the theoretically normal or enhanced gastric emptying time with cornstarch in comparison to rice or bean gum, the number of transient lower oesophageal sphincter relaxations, the major mechanism favouring GOR, is reduced. However, since neither the gastric emptying nor the transient relaxations were measured, this theoretical concept is only hypothetic.

It cannot be excluded that part of the effect observed is the consequence of the natural evolution of a decrease in regurgitation [2]. However, the significant difference in improvement between the thickened and standard formula challenges this hypothesis thoroughly.

In conclusion, this blinded, prospective, randomised trial performed with a casein dominant formula thickened with a specifically treated cornstarch shows a significant reduction in acid exposure to the oesophageal mucosa [13]. This observation cannot be confirmed with other thickening agents such as carob bean [3] or rice [13,15]. The results suggest the benefit of cornstarch over bean gum and rice starch in controlling acid reflux. Further data are needed to confirm that cornstarch is superior to rice starch or locust bean. Further data are also needed to evaluate how cornstarch decreases acid GER. Moreover, since it can be hypothesised that cornstarch thickened formula reduces both acid and non-acid reflux, future research using impedancemetry in infants with GOR-disease presenting with irritability [8] would be welcomed.

Conflict of interest statement

Two of the authors (Y.V. and B.L.L.) are scientific advisors for United Pharmaceuticals on an interim basis.

Acknowledgment

The authors are grateful to United Pharmaceuticals for providing free formula Novalac AR for the participating infants up to a maximal period of 3 months.

References

[1] Hillemeyer AC. Gastroesophageal reflux: diagnostic and therapeutic approaches? Pediatr Gastroenterol 1996;43:197–212.
[2] Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 1997;151:569–72.
[3] Vandenplas Y, Hachimi-Idrissi S, Casteels A, Mahler T, Loeb H. A clinical trial with an "anti-regurgitation" formula. Eur J Pediatr 1994;153:419–23.
[4] Vandenplas Y, Ashkenazi A, Belli D, Boige N, Bouquet J, Cadranel S. A proposition for the diagnosis and treatment of gastro-oesophageal reflux disease in children: a report from a working group on gastro-oesophageal reflux disease. Working Group of the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN). Eur J Pediatr 1993;152:704–11.
[5] Miyazawa R, Tomomasa T, Kaneko H, Morikawa A. Effect of locust bean gum in anti-regurgitant milk on the regurgitation in uncomplicated gastroesophageal reflux. J Pediatr Gastroenterol Hepatol 2004;38:479–83.
[6] Vandenplas Y, Lifshitz JZ, Orenstein S, Lifschitz CH, Shepherd RW, Casaubon PR. Nutritional management of regurgitation in infants. J Am Coll Nutr 1998;17:308–16.
[7] Iacono G, Vetrano S, Cataldo F, Siino O, Russo A, Lorello D, et al. Clinical trial with thickened feeding for treatment of regurgitation in infants. Dig Liver Dis 2002;34:532–3.
[8] Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr 2003;143:219–23.
[9] Vandenplas Y, Helven R, Goyvaerts H, Sacre L. Reproducibility of continuous 24 hour oesophageal pH monitoring in infants and children. Gut 1990;31:374–7.
[10] Vandenplas Y. ESPGHAN reflux esophagitis in infants and children: a report from the Working Group on Gastro-Oesophageal Reflux Disease of the European Society of Paediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1994;18:413–22.
[11] Vandenplas Y, Goyvaerts H, Helven R. Gastro-esophageal reflux, as measured by 24-hr pH monitoring, in 509 healthy infants screened for SIDS-risk. Pediatrics 1991;88:834–40.
[12] Wenzl TG, Schneider S, Scheele F, Sinly J, Heimann G, Skopnik H. Effects of thickened feeding on gastroesophageal reflux in infants: a placebo-controlled crossover study using intraluminal impedance. Pediatrics 2003;111:e355–9.
[13] Ramirez-Mayans J, Palacio-del Carmen L, Cervantes-Bustamante R, Mata-Rivera N, Pina-Romero N, Zarate-Mondragon F. Nutritional management of children with gastroesophageal reflux: a comparison of two different formulas. Int Pediatr 2003;18:78–83.
[14] Vandenplas Y, Sacre L. Milk-thickening agents as treatment for gastroesophageal reflux. Clin Pediatr 1996;26:66–8.
[15] Orenstein SR, Magill HL, Brooks P. Thickening of infant feedings for therapy of gastroesophageal reflux. J Pediatr 1987;110:181–6.
[16] Chevallier B, Grunberg J, Rives JJ, Van Eegroo LD, Fichot MC. Evaluation de la tolérance et de l'efficacité d'un lait épaissi à l'amidon de maïs chez le nourrisson présentant des régurgitations simples. Ann Pediatr 1998;45:509–15.

[17] Borelli O, Salvia G, Campanozzi A, Franco MT, Moreira FL, Emiliano M. Use of a new thickened formula for treatment of symptomatic gastroesophageal reflux in infants. Ital J Gastroenterol Hepatol 1997;29:237–42.

[18] Aggett PJ, Agostoni C, Goulet O, Hernell O, Koletzko B, Lafeber HL, ESPGHAN Nutrition Committee. Antireflux or antiregurgitation milk products for infants and young children: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2002;34:496–8.

[19] Bosscher D, Van Caillie-Bertrand M, Van Cauwenbergh R, Deelstra H. Availabilities of calcium, iron, and zinc from dairy infant formulas is affected by soluble dietary fibers and modified starch fractions. Nutrition 2003;19:641–5.

[20] Senterre J. Net absorption of starch in low birth weight infants. Acta Ped Scand 1980;69:653–7.

[21] Ambrosolli R, Di Stasio L, Mazzocco P. Content of alpha S1-casein and coagulation properties in goat milk. J Dairy Sci 1988;71:24–8.

[22] Lelong M, Paupe J, Colin J, Mabille H. La floculation de la caséine du lait de vache en presence des empois d'amidon: comparaison entre le tapioca et les autres amidons. Arch Fr Pédiatr 1965;4:427–39.

[23] Siegel M, Krantz B, Lebenthal E. Effect of fat and carbohydrate composition on the gastric emptying of isocaloric feedings in premature infants. Gastroenterology 1985;89:785–91.

[24] Tolia V, Lin CH, Kuhns LR. Gastric emptying using three different formula in infants with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 1992;15:297–301.