

A DOUBLE-BLIND TEST OF THE ABILITY OF LACTAGEN® FORMULA TO REDUCE SYMPTOMS OF LACTOSE INTOLERANCE

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ABSTRACT: A number of adults believe they are lactose intolerant but do not actually have impaired lactose digestion. To assess intervention outcomes, it is important to identify those who are truly lactose intolerant. We developed a summed Likert rating scale to reflect the underlying latent properties that must be inferred rather than directly observed in screening for lactose intolerance. **Subjects:** Over two hundred self diagnosed persons with lactose intolerance were recruited and pre-screened using the Likert symptom scale. The symptoms rated included bloating, abdominal pain, abdominal cramps, watery diarrhea and nausea. A score of 9 or higher combined with no information suggesting milk allergy, pregnancy, or any medical conditions that mimic lactose intolerance such as irritable bowel syndrome or other functional GI tract disorder qualified the subject for intervention. **Methods:** A double-blind experimental design was employed. Participants were paired by gender, age, and ethnicity, and then randomly assigned to Lactagen or a placebo. Both members of 27 assigned pairs completed the program and provided a second data point and both members of 26 pairs completed and provided three data points. **Results:** Lactagen's 38 day program demonstrated significant decrease in severity of all symptoms when challenged with a lactose load (8, 10, and 12 oz glass of milk) after metabolic adaptation compared with pre-adaptation severity. The present study demonstrated significant symptom improvement in 80% of those randomized to Lactagen, while only 19% improved on placebo. The study confirms the occurrence of metabolic adaptation of the colonic flora to prolonged lactose ingestion.

Objective: This research was designed to determine whether graduated and controlled administration of Lactagen® to individuals confirmed as lactose intolerant effectively relieved their symptoms of lactose intolerance.

Design: A double-blind experimental design was employed. A Likert Scale was used to score five predetermined symptoms on a scale of 0-4. Each subject rated symptoms of bloating, abdominal pain, cramps, diarrhea and nausea. A ranked scale was used: 0 indicated no symptoms, 1 indicated slight symptoms, 2 indicated mild symptoms, 3 indicated moderate symptoms, and 4 indicated severe symptoms. Thus, the maximum possible score is 20. A score of 9 or higher combined with no information suggesting milk allergy, Irritable Bowel Syndrome (IBS) or pregnancy qualified the subject for participation. Subjects were paired by age group (18-25; 26-44; and 45-55) and gender.

Subjects: Subjects were recruited from the greater Los Angeles area. Participants reporting 55% of maximum symptoms on a Likert scale (based on reports from 312 previous Lactagen users) were eligible for the study. Each qualified subject was given detailed instructions regarding the program,

including a discussion of benefits and risks. Subjects signed an informed consent and the study was approved by the Institutional Review Board Committee at the Ventura County Medical Center. Eighty-five lactose intolerant individuals between the ages of 18-55 qualified to participate in the study. Forty pairs of matched (age group, gender, and ethnicity) subjects were enrolled and followed the 38-day Lactagen program with either a placebo or the product itself. Both the subject and the physician responsible for administration of screening and informed consent procedures was unaware of whether Lactagen or the placebo was provided to the subject. To insure proper administration of the product/placebo and evaluation of compliance, each subject was asked to keep a daily log recording food, preparation dosage taken and any symptoms experienced while on the program. The research director along with trained staff contacted each subject once a week for the first two weeks and then once every other week thereafter, to check on their progress by telephone or Email. Questions were answered almost immediately and directions were provided on a personal basis if any changes were needed.

BACKGROUND

Lactose intolerance is one of the most common gastrointestinal disorders, estimated to affect more than 50 million Americans.¹ This condition arises from an enzyme (lactase) deficiency in the gut. Without adequate amounts of lactase, the digestive system is unable to properly break down and absorb lactose, the main sugar in milk and dairy products. When this happens, lactose is fermented by bacteria in the colon, causing symptoms of bloating, diarrhea, flatulence, and abdominal cramps. It is the most common type of malabsorption because milk sugar is common in a typical diet. Lactase retention is genetically determined as a dominant trait. Lactase reaches its maximum levels in the human intestine shortly after birth and declines after the age of 3 ½.² Worldwide, humans lose 90 to 95 percent of birth lactase levels by early childhood, and there is a continuous decline in lactase during the course of a lifetime.³

Ethnic groups in the United States who have the greatest percentages of lactose intolerance⁴ are:

- 90% Asian Americans
- 80% African Americans
- 53% Hispanic Americans
- 25% Caucasians

Caucasians have the lowest rate of lactose intolerance in the United States due to the prevalence of milk in Northern European diets. Indeed, Northern Europeans have the lowest rate of lactose intolerance across the globe.

There are degrees of carbohydrate intolerance. Some individuals manufacture a small amount of the enzyme, while others lack the enzyme completely. Any degree will result in malabsorption.⁵

Recent evidence^{(6) (7) (8) (9) (10)} suggests that patients with medically confirmed lactose malabsorption can ingest the number of servings of milk and dairy products recommended by the American Dietetic Association without experiencing gastrointestinal discomfort. Some patients increase their tolerance to lactose with repeated intake.^{(6) (10)}

Product: Lactagen is a natural dietary supplement that is synthesized from Lactose, Lactobacillus Acidophilus, Tricalcium Phosphate, FOS,

Cellulose Gum and Silica that does not present any risks of toxicity to patients. Lactagen comes in powder form.

Lactagen is dissolved in 4 to 6 ounces of water and taken with meals. Patients refrain from ingesting any dairy products during the program unless specifically stated in the protocol. Lactagen formula is taken with dinner for 18 days, and then coupled with breakfast and dinner for another 16 days. During the final 4 days, milk is added to the diet. After the 38 day process, there is a slow daily re-introduction of dairy products into the diet. The complete Lactagen process takes 38 days.

Primary outcome measures: A pre and post Likert Scale was used to determine severity of five pre-determined symptoms. The analytic power was calculated to detect significant change for self-reported symptom reduction of 40% (or more) percent in the Lactagen group versus a 15% (or less) reduction in the placebo group.

STATISTICAL ANALYSIS

The data collected from the symptom scores sheets were analyzed. Data analysis focused on reported before, immediately following and one month symptom score sheets combined with group (Lactagen or placebo) designation. Based on a limited number of pilot test subjects, a total of 30 subjects in each group were to have complete the study protocol for adequate statistical power to observe statistically significant differences between groups at $p > .05$. Each subject had the option of dropping out at any time, in which case his or her data was excluded from the final assessment.

SUMMARY OF AVAILABLE DATA POINTS

The data collection was successful. Participants provided ratings for five symptoms of lactose intolerance on a 0 (no symptom) to 4 (severe symptom) scale. Therefore, the total symptom scale provided scores ranging from 0 to 20. In all, data were collected pre-treatment for 85 individuals and 64 individuals (75.3%) completed the program and provided data at the conclusion of that program. A total of 44 and 41 were randomized to Lactagen and Placebo, respectively. Completion rates were 72.7% for those assigned to the Lactagen group and 78% for those assigned to the placebo group. Further, 61 individuals provided data between one and two months following completion of the program.

Participants were paired by gender, age, and ethnicity, and then randomly assigned to Lactagen or a placebo. Both members of 27 assigned pairs completed the program and provided a second data point, and both members of 26 pairs completed all three data points.

For the 32 Lactagen group members, 56.3% were male and the average age of subjects was 36.7 years (standard deviation = 22.6). For the 32 Placebo group members, 56.3% were male and the average age was 36.4 years (standard deviation = 20.8). For both groups, 40 years of age was the median. The ethnicity breakdowns for the Lactagen and Placebo groups are shown below.

Ethnicity	Treatment (N=32)	Placebo (N=32)
Asian	21.9%	15.6%
African American	25.0%	25.0%
Latino	15.6%	25.0%
White	37.5%	34.4%

SUMMARY OF RESULTS

In this section, data are summarized for all individuals that provided information for two or more data points (Table 1). At the pre-treatment measurement point, members of the two groups provided statistically equivalent ratings of their symptoms for lactose intolerance ($t = 0.95$, n.s.)¹. At the post treatment measurement point, the Lactagen group provided symptom ratings that, in total, were 54.6 percent lower than their original ratings, while the placebo group ratings declined by 34.1 percent. At post-treatment, analyses (analysis of covariance employing the pre-treatment ratings as the covariate) indicated that the respondents provided with Lactagen reported a significant decline in symptoms relative to the placebo group ($F = 8.81$, $p > .01$). Approximately one month later, participants were contacted again.

¹ t and F are statistics that are used to determine whether two (or more) groups differ in their mean scores on a measurement. “n.s.” indicates that the two groups were not statistically different from each other. “ $p > .01$ ” indicates that the likelihood of the two group measures differing by the observed amount is less than 1 in 100, and “ $p > .001$ ” indicates a chance likelihood of less than 1 in 1000.

At that point, the Lactagen group provided symptom ratings that were 56.6 percent lower than their original ratings, while the placebo group ratings declined by only 23.3 percent. Again, these results were significantly different ($F = 18.32$, $p > .001$). As well, the percentage of respondents with a decline of 10 or more points (or one-half the maximum reduction possible for the rating scale employed) on the total ratings were examined. As would be expected, the results were similar. For the post-treatment measurement point, 71.9 percent of the Lactagen group, but only 37.5 percent of the placebo group reported symptom declines of 10 points or greater on the rating scale ($\chi^2 = 7.63$, $p > .01$)². One month later, the observed differences had increased, and 79.3 percent of the Lactagen group but only 18.8 percent of the placebo group reported a symptom rating scale decline of at least 10 points ($\chi^2 = 22.37$, $p > .001$).

Table 1

Summary of data for participants providing symptom ratings for 2 or more data points

	Pre-Treatment		Post-Treatment		1-month follow-up	
	N	Mean (s.d.)	N	Mean (s.d.)	N	Mean (s.d.)
Lactagen	32	14.1 (2.6)	3 2	3.7 (5.6)	2 9	3.3 (5.8)
Placebo	32	14.9 (3.5)	3 2	8.1 (6.2)	3 2	10.3 (5.6)

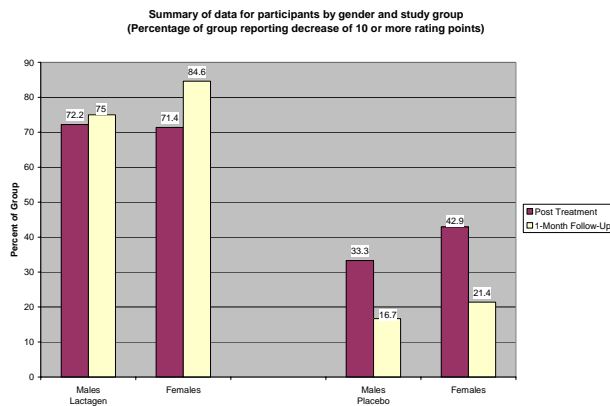
Analysis of reported decreases in symptoms by gender indicated that both males and females benefited in similar proportions at both post-program data points in the Lactagen group. Further, the decline in perceived “effectiveness” of the program (from the immediate post-program report until one month later) in the Placebo group was similar for both males and females (Table 2).

² χ^2 (chi-square) is a measure of association indicating to what degree group membership is associated with a particular result, such as a decline of more than 5 points on a rating scale.

Table 2

Summary of data for participants by gender and study group (Percentage of group reporting decrease of 10 or more rating points).

	Post-Treatment Gender	Percent of Group	1-month follow-up Percent of Group
Lactagen	Males (N=18)	72.2%	75.0%
	Females (N=14)	71.4%	84.6%
Placebo	Males (N=18)	33.3%	16.7%
	Females (N=14)	42.9%	21.4%



Examination of participant symptom reports by age group also provided a similar pattern for the Lactagen group participants. That is, the proportion of both younger and older participants reporting a large decrease in symptoms increased between immediate post-treatment and one-month follow-up data collection. For the Placebo group, there was a tendency for participants under 40 years old to report greater “benefit” from the program than for those over 40.

Table 3

Summary of data for participants by age and study group (Percentage of group reporting decrease of 10 or more rating points).

	Post-Treatment Age	Percent of Group	1-month follow-up Percent of Group
Lactagen	Under 40 (N=16)	68.8%	81.3%
	40 and over (N=16)	75.0%	76.9%
Placebo	Under 40 (N=15)	47.1%	29.4%
	40 and over (N=17)	26.7%	6.7%

CONCLUSION

Lactose intolerance is one of the most common gastrointestinal disorders; however the symptomatic expression of lactose intolerance is relatively less prevalent. Most people who are lactose intolerant can consume one glass of milk per day asymptotically¹¹. The amount of ingested lactose required to produce symptoms is reported to be about 12 to 18 g, or 8 to 12 oz of milk. Several factors affect the severity of symptoms after lactose ingestion, including the patient's ethnic origin and age; older patients are more susceptible. The mechanisms by which this occurs are not yet completely understood, but one mechanism should be attributed to the role of colonic bacteria in carbohydrate malabsorption¹². Lactase and sucrase isomaltase, which are found in the lining of the small intestine, acts to break down complex sugars. In the large intestine, water is absorbed and indigenous microflora metabolizes lactose into gases (H₂, CH₄ and CO₂) and easily absorbable metabolites such as short-chain fatty acids (SCFA). This reduces the osmotic load of the unabsorbed sugar and prevents an increase in fecal water. Recent studies have suggested that reduced colonic capacity for fermentation and decreased levels in short chain fatty acids (SCFA) are responsible for both carbohydrate-induced and antibiotic-associated diarrhea^{13, 14}. On the other hand, factors that cause an increase in fermentation and SCFA production may contribute to suppression or mitigation of lactose intolerance. It is postulated that lactobacilli supplementation could enhance lactose fermentation and thus improve lactose intolerance. Lactobacilli have been shown to survive through the gastrointestinal tract and adhere to intestinal tissue and human cells^{15,16}. Because *Lactobacillus acidophilus*

is indigenous to the large intestine and readily ferments lactose without H₂ production, the survival or colonization of exogenous *L. acidophilus* in the colon could, theoretically, enhance lactose fermentation by supplementing additional β-gal activity or by interacting with the indigenous microflora. The colonic flora readily adapts to lactose in the diet of maldigesters. Thus, routine consumption of lactose produces fewer symptoms due to more efficient metabolism of lactose by the colon microflora.

In summary, the present study demonstrated significant symptom improvement in 80% of those randomized to Lactagen, while only 19% improved on placebo. The present study confirms the occurrence of metabolic adaptation of the colonic flora to prolonged lactose ingestion (ie. a formulated product like Lactagen). Lactagen acts to promote the growth of indigenous microflora needed to metabolize lactose. A significant decrease in the severity of all symptoms was reported by participants in Lactagen's 38 day program when challenged with a lactose load (8, 10, and 12 oz glass of milk) after metabolic adaptation compared with pre-adaptation severity. Post one month data demonstrated a continued (and increased) degree of improvement as subjects continued to incorporate dairy products into their diets. Neither gender nor age was a factor in the overall results. Our study would infer that through the Lactagen these bacteria are sustained in over 80% of the graduates of the program.

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