Digestive Diseases and Sciences, Vol. 49, No. 1 (January 2004), pp. 73–77 (© 2004)

A 14-Day Elemental Diet Is Highly Effective in Normalizing the Lactulose Breath Test

MARK PIMENTEL, MD, FRCP(C), TESS CONSTANTINO, RN, YUTHANA KONG, MPH, MEERA BAJWA, MD, ABOLGHASEM REZAEI, MD, and SANDY PARK, BA

Treatment of small intestinal bacterial overgrowth is frustrated by the low efficacy of antibiotics. Elemental diets have been shown to reduce enteric flora. In this study, we evaluate the ability of an elemental diet to normalize the lactulose breath test (LBT) in IBS subjects with abnormal breath test findings. Consecutive subjects with IBS and abnormal LBT suggesting the presence of bacterial overgrowth underwent a 2-week exclusive elemental diet. The diet consisted of Vivonex Plus (Novartis Nutrition Corp., Minneapolis, MN) in a quantity based on individual caloric requirement. On day 15 (prior to solid food), subjects returned for a follow-up breath test and those with an abnormal LBT were continued on the diet for an additional 7 days. The ability of an elemental diet to normalize the LBT was determined for days 15 and 21. A chart review was then conducted to evaluate any clinical benefit 1 month later. Of the 93 subjects available for analysis, 74 (80%) had a normal LBT on day 15 of the elemental diet. When those who continued to day 21 were included, five additional patients normalized the breath test (85%). On chart review, subjects who successfully normalized their breath test had a $66.4 \pm 36.1\%$ improvement in bowel symptoms, compared to $11.9 \pm 22.0\%$ in those who failed to normalize ($P < 0.001$). An elemental diet is highly effective in normalizing an abnormal LBT in IBS subjects, with a concomitant improvement in clinical symptoms.

KEY WORDS: bacterial overgrowth; enteral nutrition; elemental diet; irritable bowel syndrome.

Bacterial overgrowth is a condition whereby the bacteria of the normally colonized colon are now also colonizing the relatively sterile small intestine. The resulting displacement of bacteria into the small bowel produces a constellation of symptoms including altered bowel habits, abdominal pain, bloating, gas, and distention (1). Classically, bacterial overgrowth is observed in subjects with altered bowel anatomy (2–8). However, recent data suggest that the majority of subjects with IBS may also have an abnormal lactulose breath test (LBT) to suggest bacterial overgrowth in the absence of underlying bowel disease (9, 10). Although there remains some argument as to whether the abnormal LBT in IBS represents accelerated transit or abnormal small bowel flora, IBS symptoms respond to a normalization of the breath test with antibiotics and the LBT abnormality in IBS is significantly different from controls (10).

One major problem in the management of bacterial overgrowth is the poor success of antibiotics in eliminating the large variety of organisms present. In fact, recent studies show that, at best, norfloxacin and ampicillin-clavulanate have a 30 and 50% success in normalizing the LBT to indicate eradication of bacterial overgrowth, respectively (11). This and other experiences lead clinicians to use rotating antibiotics, prolonged courses, and repeated treatment that potentially lead to bacterial resistance. In the case of IBS, neomycin is successful in normalizing the LBT in only 20% of subjects receiving

Manuscript received June 21, 2003; accepted September 30, 2003.

All from the GI Motility Program, Division of Gastroenterology, Department of Medicine, Cedars-Sinai Medical Center, CSMC Burns & Allen Research Institute, Los Angeles, California 90048, and School of Medicine, University of California, Los Angeles, California 90024, USA.

Address for reprint requests: Mark Pimentel, MD, Cedars-Sinai Medical Center, 8635 West 3rd Streets, Suite 770 W, Los Angeles, California 90048, USA; mark.pimentel@cshs.org.

the therapy (10). Since IBS is present in more than 10% of the population as a whole (12), widespread antibiotic use in this condition is not wise. As such, a better therapy is needed for bacterial overgrowth and IBS subjects with abnormal LBT that is more reliable and avoids excessive antibiotic use.

Elemental enteral formulations are believed to be entirely absorbed within the first few feet of small intestine. As such, there is a potential for this diet to limit the nutrients for more distally located bacteria of the small intestine. Early research suggests that elemental formulae are capable of reducing stool microbes (13–15). The basis for this change in flora is postulated to be due to nutrient deprivation.

Based on the potential effect of this diet, we hypothesize that a prolonged elemental diet may normalize the LBT finding in IBS subjects and perhaps even supercede antibiotics in treatment efficacy.

METHODS

Patient Population. This was a retrospective review of consecutive cases where elemental diet was used to attempt normalization of LBT in subjects with IBS and abnormal LBT. From 2001 to 2002, subjects who were diagnosed with IBS based on Rome I criteria underwent a LBT. Most subjects found to have an abnormal LBT were then given a trial of antibiotic therapy. After failed attempts to normalize the LBT with antibiotics, subjects were presented the option of the elemental diet since, in preliminary experiences, we had observed normalization of LBT as well as a dramatic clinical response with this therapy.

Elemental Diet. Subjects agreeing to undergo the diet met with the GI motility nurse at Cedars-Sinai Medical Center (T.C.). Based on the height and weight of each subject, the caloric requirement was calculated using the Harris–Benedict equation (16). Subjects then purchased Vivonex Plus (Novartis Nutrition Corp., Minneapolis, MN) in the predetermined quantity. Flavor packets were also used as desired. Patients were all given instructions to dissolve the powdered packets of Vivonex Plus into 250 ml of warm water, add ice, and blend for 1 min. In general, subjects were asked to create three meals a day by dividing the daily recommendations into three equal servings.

Subjects then took the elemental formulation for a period of 14 days. During that time, no food ingestion was allowed including gum, candy, soft drinks (diet or otherwise), and caffeine. Any prescription medications were continued throughout the course.

On day 15, subjects returned for a follow-up LBT. If the LBT was still abnormal on day 15, subjects were encouraged to persist with the diet for an additional 7 days, followed by another LBT. No patient was asked to continue beyond 21 days.

Lactulose Breath Testing. For the LBT, subjects were asked to fast from 7 PM the night before the test. They were also asked to avoid heavy proteins or legumes in the previous evening's meal. On the day of testing, subjects presented to the GI Motility Lab at Cedars-Sinai Medical Center. After an initial breath sample was collected, subjects were asked to ingest a syrup containing 10 g of lactulose (Inalco Spa, Milano, Italy, packaged by Xactdose Inc., South Beloit, IL). After ingestion, breath samples were taken every 15 min until 180 min had elapsed. All breath samples were alveolar and analyzed using a Model SC Quintron Gas Chromatograph (Quintron Instrument Co., Milwaukee, WI). This was used to determine the concentration of hydrogen and methane in breath samples after correction for alveolar quality using the CO_2 concentration in the breath sample. Values for hydrogen and methane were plotted graphically over time. A normal breath test was defined as one that exhibited a rise of breath hydrogen or methane never >20 ppm with the rise beyond 90 min after the ingestion of lactulose (11). All breath tests were coded and randomized. A blinded reader (M.P.) interpreted all results as normal or abnormal. The success of the elemental diet was then determined.

Clinical Outcomes. As part of their clinical care, patients completing the elemental diet were encouraged to return for a follow-up outpatient evaluation at 1 month after completion. Although not initially designed to be a prospective study, during the clinic visit, an attempt was made to quantify any improvement quantitatively (percentage improvement) or qualitatively. A retrospective chart review was conducted on these subjects to define the clinical outcomes in their IBS symptoms from this treatment.

Other specific information was also collected from the chart review. This information included identifying the response among IBS subgroups and identifying the reason for using vivonex, and an attempt was made to determine why any failure of the elemental diet might have taken place.

Statistical Analysis. The proportion of subjects normalizing their LBT was evaluated at day 15. The additional benefit of continuing the elemental diet for an additional 7 days among those who did not normalize at day 15 was also evaluated. The LBT profile was compared before and after the elemental diet, with each time point being compared using a *t*-test. Data are expressed as mean $\pm$ SE.

RESULTS

Patient Population. At the time of review, 124 IBS subjects with an abnormal LBT had agreed to try the elemental diet. Of these subjects, 14 were excluded from analysis, as they could not tolerate the diet and dropped out before completion of the 14 days. In 15 other subjects, the day 15 breath test could not be found. Some of these subjects included out-of-city/state referred patients who did not have access to convenient breath testing. Two other patients had only the day 15 breath test and not the initial breath test. Since the initial abnormal breath test could not be confirmed, these too were excluded. This left 93 subjects for analysis.

Success of the Elemental Diet. By day 15, 74 of the 93 (80%) subjects receiving the elemental diet normalized their LBT. Of the 19 subjects who did not normalize the LBT by day 15, data were available for 17 subjects on day 21. Of these 17 subjects, only 5 additional subjects normalized their LBT with the extended course. The combined success rate for the 14-day and extended course of elemental diet was then 79 of 93 subjects (85%).

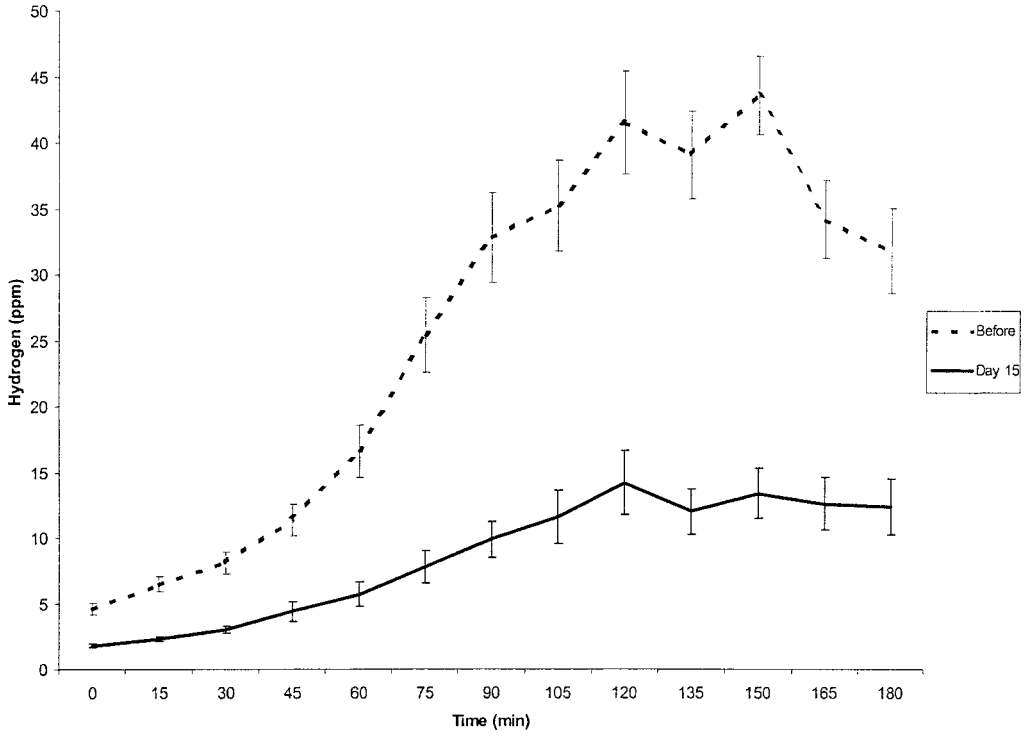

Fig 1. Comparison of lactulose breath test profiles before and after 14 days of Vivonex Plus.

When the actual LBT plot of hydrogen was compared before and after 14 days of elemental diet, all time points were significantly improved among the 93 subjects (Figure 1).

Clinical Outcomes. As far as clinical outcomes were concerned, of 93 subjects, 63 returned for their 1-month follow-up. Of the 63 subjects undergoing elemental diet with clinical follow-up, 13 chose to use the diet without any attempt at antiobiotics. The remaining 50 subjects had failed antibiotic treatment as a reason for choosing the diet.

Among the 63 returning for follow-up, 52 (83%) successfully eradicated. This rate of eradication was identical to that of the whole group, indicating that failure to eradicate was not the reason subjects did not return for follow-up.

Of 63 subjects, quantitative improvement was documented in the chart for 36 subjects, and of these 36 subjects, 28 had documented normalization of LBT with elemental diet. The percentage improvement in IBS symptoms among those who normalized was $66.4 \pm 36.1\%$, compared to $11.9 \pm 22.0\%$ in those who failed to normalize ($P < 0.001$).

On evaluating IBS by subgroup among the 52 subjects with successful eradication after elemental diet, 14 were diarrhea predominant, 25 were alternators, 12 had constipation-predominant IBS, and 1 had only bloating as the main concern. Of the 14 diarrhea-predominant subjects, 12 reported having regular bowel movements at 1-month follow-up and 1 still had diarrhea (1 had no indication of status). In the group of alternators, 18 had regular bowel movements after the diet, 4 said they felt better, 1 felt the same, and 2 were not sure. Among the 12 constipation predominant, 9 were regular, 2 continued to have constipation, and 1 was not sure.

On trying to identify the reason for failure of the elemental diet, subjects who failed to eradicate their overgrowth ($n = 11$) were reviewed. At the time of the review, three of these subjects had confirmed or suspected inflammatory bowel disease, one has since been found to have colonic inertia, one had adhesions from a previous surgery, and one was noncompliant with the elemental diet. Any possible explanation for failed therapy in the remaining five was unknown.

DISCUSSION

To our knowledge this is the first successful use of a short-term elemental diet in normalizing the LBT for the treatment of bacterial overgrowth. Vivonex Plus is able to normalize a preexisting abnormal LBT in 80% of subjects after 14 days of therapy. This benefit is far greater than that seen for antibiotics (10, 11). Furthermore, this normalization of LBT translated into a clinical benefit.

Elemental formulations have been available for more than two decades. An elemental diet formulation consists of hydrolyzed nutrients such that digestion of the product by the recipient will be minimal. The obvious application of this type of formulation is in subjects with a compromised or foreshortened digestive system where formal digestion is compromised. In the 1980s and early 1990s, there was interest in the use of elemental diet for subjects with Crohn's disease (17). Although the results were mixed, data seemed to suggest a benefit, and in some studies, an elemental diet fared as well as steroids in inducing remission (18–20). The mechanism of this beneficial effect was perceived to be related to "bowel rest" rather than the nutritional reconstitution of the subject (21). Interestingly, most contemporary theories of IBD demand the presence of lumenal bacteria as a necessary antigenic stimulation without which there would be little or no inflammation in these disorders. The effect we saw in the normalization of LBT and suspected elimination of small intestinal bacteria may suggest a bacterial mechanism by which elemental diets positively influence Crohn's disease.

In the case of bacterial overgrowth, the hypothesized mechanism for the use of an elemental diet is based on the rapid absorption and assimilation of the elemental formulation. If it is quickly absorbed, there may be little available substrate for the bacteria, which we expect is more distally located in the small intestine of IBS subjects. This explanation may, however, be overly simplistic. Three other explanations are possible with some support from the literature. It is well recognized that bile and its contents have some influence on small bowel bacteria. Bile has stimulatory effects on phase III of the migrating motor complex (22). Phase III, otherwise known as the "intestinal housekeeper" is a cycling wavefront responsible for cleansing the small bowel between meals (23). The absence of phase III is known to result in small intestinal bacterial colonization (24–27). Two studies demonstrate that the ingestion of an elemental diet can produce a dramatic increase in CCK and consequently gallbladder emptying (28, 29). Therefore, one might hypothesize that the increased bilious fluid due to elemental formula ingestion would stimulate phase III, leading to a reduction in small bowel flora.

A second possible mechanism for bacterial suppression with this diet may relate to the mucosal immune system. Data suggest that this same diet can accentuate jejunal secretion of immunoglobulins (30). In the study by Colombel et al., 20 min after jejunal perfusion of an elemental diet, lumenal IgG, IgA, and albumin were significantly increased. Based on this, it is possible that the immune effects of elemental diet are beneficial in clearing the small bowel of organisms.

Finally, elemental formulations may directly affect bacteria of the GI tract. Early observations of the effect of an elemental diet on stool microflora show that this diet significantly reduces coliforms, enterococci, and bacteroides (13). The same study showed that the longer subjects were on the diet, the lower the bacterial counts. Other studies have confirmed these data (14, 15, 31, 32). Even more interesting is that, even when the duodenum is colonized with bacteria, an elemental diet can reduce or eliminate the organisms (31). Since one would expect the duodenum to be exposed to the nutrient composition of the elemental feeding, nutrient deprivation would not explain the reduction of duodenal flora seen. Perhaps the composition of the elemental formula itself has inhibiting effects on bacteria.

Another important point from this study is the continued finding that normalization of the LBT determines the outcome of IBS symptoms. This is consistent with the previous findings by our group (10). The current paper also shows that all subgroups of IBS have a benefit, including the diarrhea, constipation, and alternating subgroups.

In conclusion, an elemental diet is capable of normalizing an abnormal LBT in a much greater proportion of patients than antibiotics. The mechanism of this effect is unclear but likely is not as simple as nutrient deprivation of the bacterial organisms. This treatment appears also to be a viable alternative to antibiotics. In addition, the diet has clinical benefits as evidenced by 1-month follow-up which depends on its ability to normalize the LBT.

ACKNOWLEDGMENT

This work was supported in part by the Beatrice and Samuel A. Seaver Foundation.

REFERENCES

1. Yamada T, Alpers DH, Owyang C, et al.: Textbook of Gastroenterology, 2nd ed. Philadelphia, J. B. Lippincott, 1995
2. Deitch EA, Bridges WM, Ma JW, et al.: Obstructed intestine as a reservoir for systemic infection. Am J Surg 159:394–401, 1990
3. Browning GG, Buchan KA, Mackay C: The effect of vagotomy and drainage on the small bowel flora. Gut 15:139–142, 1974
4. Greelee HB, Gelbart SM, DeOrio AJ, et al.: The influence of gastric surgery on the intestinal flora. Am J Clin Nutr 30:1826–1833, 1977
5. Enander LK, Nilsson F, Ryden AC, et al.: The aerobic and anaerobic microflora of the gastric remnant more than 15 years after Billroth II resection. Scand J Gastroenterol 17:715–720, 1982
6. Bergesen O, Schjonsby H, Schjerven L: Is vitamin B12 malabsorption in bile fistula rats due to bacterial overgrowth? A study of bacterial metabolic activity in the small bowel. Scand J Gastroenterol 23:471–476, 1988
7. Griffin WO Jr, Richardson JD, Medley ES: Prevention of small bowel contamination by ileocecal valve. South Med J 64:1056–1058, 1971

8. Rutgeerts P, Ghoos Y, Vantrappen G, et al.: Ileal dysfunction and bacterial overgrowth in patients with Crohn's disease. Eur J Clin Invest 11:199–206, 1981
9. Pimentel M, Chow EJ, Lin HC: Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol 95:3503–3506, 2000
10. Pimentel M, Chow EJ, Lin HC: Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: A double-blind, randomized, placebo-controlled study. Am J Gastroenterol 98:412–419, 2003
11. Attar A, Flourie B, Rambaud JC, et al.: Antibiotic efficacy in small intestinal bacterial overgrowth-related chronic diarrhea: a crossover, randomized trial. Gastroenterology 117:794–797, 1999
12. Talley NJ, Zinsmeister AR, Van Dyke C, et al.: Epidemiology of colonic symptoms and the irritable bowel syndrome. Gastroenterology 101:927–934, 1991
13. Winitz M, Adams RF, Seedman DA, et al.: Studies in metabolic nutrition employing chemically defined diets. Am J Clin Nutr 23:546–549, 1970
14. Bounous G, Devroede GJ: Effects of an elemental diet on human fecal flora. Gastroenterology 66:210–214, 1974
15. Dickman MD, Chappelka AR, Schaedler RW: Evaluation of gut microflora during administration of an elemental diet in a patient with an ileoproctostomy. Dig Dise 20:377–380, 1975
16. Harris JA, Benedict FG: A Biometric Study of Basal Metabolism in Man. Publ 270 Carnegie Institute of Washington, Washington, DC, 1919
17. Bernstein CN, Shanahan F: Braving the elementals in Crohn's disease. Gastroenterology 103:1363–1364, 1992
18. Gorard DA, Hunt JB, Payne-James JJ, Palmer KR, et al.: Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. Gut 34:1198–1202, 1993
19. Papadopoulou A, Rawashdeh MO, Brown GA, et al.: Remission following an elemental diet or prednisolone in Crohn's disease. Acta Paediatr 84:79–83, 1995
20. Zoli G, Carè M, Parazza M, et al.: A randomized controlled study comparing elemental diet and steroid treatment in Crohn's disease. Aliment Pharmacol 11:738–740, 1997
21. Teahon K, Pearson M, Smith T, et al.: Alterations in nutritional status and disease activity during treatment of Crohn's disease with elemental diet. Scand J Gastroenterol 30:54–60, 1995
22. Szurszewski JH: A migrating electric complex of the canine small intestine. Am J Physiol 217:1757, 1969
23. Christensen J: Intestinal motor physiology. *In* Gastrointestinal and Liver Disease, 6th ed. Feldman M, Scharschmidt BF, Sleisenger MH (eds.) Philadelphia, W. B. Saunders, p 1443, 1998
24. Vantrappen G, Janssens J, Hellemans J, et al.: The interdigestive motor complex of normal subjects and patients with bacterial overgrowth of the small intestine. J Clin Invest 59:1158–1166, 1977
25. Scott LD, Cahall DL: Influence of the interdigestive myoelectric complex on enteric flora in the rat. Gastroenterology 82:737–745, 1982
26. Kueppers PM, Miller TA, Chen CY, et al.: Effect of total parenteral nutrition plus morphine on bacterial translocation in rats. Ann Surg 217:286–292, 1993
27. Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, et al.: The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. Ann Surg 228:199–193, 1998
28. Watanabe S, Shiratori K, Takeuchi T, et al.: Release of cholecystokinin and exocrine pancreatic secretion in response to an elemental diet in human subjecsts. Dig Dis Sci 31:919–924, 1986
29. Hopman WPM, de Jong AJL, Rosenbusch G, et al.: Elemental diet stimulates gallbladder contraction and secretion of cholecystokinin and pancreatic polypeptide in man. Dig Dis Sci 32:45–49, 1987
30. Colombel JF, Vaerman JP, Hällgren R, et al.: Effect of intrajejunal elemental diet perfusion on jejunal secretion of immunoglobulins, albumin and hyaluronan in man. Gut 33:44–47, 1992
31. Axelsson CK, Justesen T: Studies of the duodenal and fecal flora in gastrointestinal disorders during treatment with an elemental diet. Gastroenterology 72:397–401, 1977
32. Van der Linden W, Marsell R: Pneumatosis cystoides coli associated with high H2 excretion: Treatment with an elemental diet. Scand J Gastroenterol 14:173–174, 1979