Failure to improve parameters of lactose maldigestion using the multiprobiotic product VSL3 in lactose maldigesters: A pilot study

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Lactose maldigestion is a common genetic trait in up to 70% of the world's population. In these subjects, the ingestion of lactose may lead to prebiotic effects which can be confirmed by measurement of breath hydrogen. After a period of continuous lactose ingestion, colonic bacterial adaptation is measurable as improved parameters of lactose digestion. There may be inherent benefits in this process of adaptation which may protect against some diseases. We attempt to link therapeutically beneficial probiotics (VSL3, Seaford Pharmaceuticals Inc, Ontario) with improvement in parameters of lactose maldigestion. Two groups of five subjects with maldigestion were fed one or four packets of VSL3 (one packet containing 450×10^9 live bacteria) before testing and then 17 days later. A 50 g lactose challenge was carried out before and after feeding. While there was a trend toward increasing rather than reducing of summed breath hydrogen, no statistically significant changes were observed between results from before testing and those from testing 17 days later. The authors conclude that direct consumption of the probiotic VSL3 may not improve parameters of lactose maldigestion without metabolic activation. In its present format, therefore, the test for colonic adaptation cannot be used to demonstrate direct bacterial embedding with VSL3.

Key Words: *Lactose intolerance; Probiotics therapy*

L'incapacité d'améliorer les paramètres de la mauvaise digestion du lactose au moyen du VSL3, un produit multiprobiotique, chez ceux qui le digèrent mal : Un projet-pilote

La mauvaise digestion du lactose est une caractéristique génétique courante, atteignant jusqu'à 70 % de la population mondiale. Chez ces sujets, l'ingestion de lactose peut provoquer des effets prébiotiques qui peuvent être confirmés par la mesure de l'hydrogène respiratoire. Après une période d'ingestion continue de lactose, l'adaptation bactérienne du côlon peut être mesurée sous forme d'amélioration des paramètres de digestion du lactose. On peut remarquer des bénéfices inhérents à ce processus d'adaptation qui peut assurer une protection contre certaines maladies. Nous tentons de relier des probiotiques au potentiel bénéfique (VSL3, Seaford Pharmaceuticals Inc., Ontario) à l'amélioration des paramètres de mauvaise digestion du lactose. Deux groupes de cinq sujets ayant des troubles digestifs ont reçu un ou quatre paquets de VSL3 (un paquet correspondant à 450×10^9 bactéries vivantes) avant le test, puis 17 jours plus tard. Une provocation par 50 g de lactose a été effectuée avant et après l'ingestion. Bien qu'on ait remarqué une tendance vers l'accroissement plutôt que la diminution de l'hydrogène respiratoire total, aucune modification statistiquement significative n'a été observée entre les résultats obtenus avant le test et ceux obtenus 17 jours plus tard. Les auteurs concluent que la consommation directe du probiotique VSL3 n'améliore peut-être pas les paramètres de mauvaise digestion du lactose sans activation métabolique. Ainsi, dans sa forme actuelle, le test d'adaptation du côlon ne peut être utilisé pour démontrer un enrobage bactérien direct par le VSL3.

The concept of prebiotics was suggested by Gibson and Roberfroid (1). It is based on the theory that some undigested nutrients (usually polysaccharides) which bypass the upper gastrointestinal tract specifically alter the metabolism and expand bacterial populations (usually lactic acid-producing bacteria) thought to exert beneficial effects on the host. There are a number of known natural (those found in leeks, hickory, onions [1] and breast milk [2]) and manufactured (eg, transgalactoliposaccharides [3] and lactulose [4]) prebiotics. Lactose in lactose maldigesters (lactase nonpersistent [LNP] subjects) may be a conditional natural prebiotic because approximately 67% to 70% of the world's population lose the ability to digest lactose (5). In these LNP subjects it has been reported that continued lactose consumption leads to improved handling of the disaccharide (6,7). The phenomenon of improved lactose tolerance on rechallenge after consuming lactose for a defined period of consumption is putatively due to colonic bacterial alteration of metabolism and expansion of targeted microbial flora (7,8). This process is termed colonic adaptation and is defined clinically by reduced measured breath hydrogen (H_2) after rechallenge with the target sugar (in this case lactose) (7). Improved symptoms of intolerance and increased fecal β-galactosidase also constitute part of adaptation. In vitro data suggest that adding *Lactobacillus* or *Bifidobacteria* species to an adapting system facilitates lactose digestion (9,10). Furthermore, there is a single study suggesting that H_2 production is reduced on lactulose rechallenge after consuming lactobacillus parvum 299V (11). Lactulose and lactose may exert similar effects on colonic bacteria (12).

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Although beneficial in its own right (improved nutritional assimilation) the process of adaptation and measurement of resulting breath H_2 may be used as a functional test of colonic bacterial status. For example, we recently showed that patients with inflammatory bowel disease (IBD) in remission are slow or unable to adapt to lactulose, as are healthy controls based on the above outlined concept (13). This adaptive test supports the notion that flora in IBD is abnormal (14,15).

In an effort to further evaluate the potential of colonic adaptation as a biological test of colonic floral function we attempted to link the test with a probiotic of suggested benefit in IBD. The eight-probiotic-containing product VSL3 (Seaford Pharmaceucticals Inc, Ontario) has been shown to be therapeutically useful in pouchitis (16,17) and ulcerative colitis in remission (18,19), and preliminary data show benefit in active ulcerative colitis (20). We therefore undertook a small pilot study and fed two doses of VSL3 to subjects with known lactose maldigestion. However, no improvement was found.

SUBJECTS AND STUDY DESIGN

Ten healthy paid volunteers of multiethnic origin who were previously established to be lactose maldigesters (four men, six women; mean age of 38.6±14.6 years) were recruited. The subjects underwent two lactose (50 g) challenge tests. The first was followed by ingestion of VSL3 bacteria and then a second similar challenge test was carried out at the end of the adapting period after 17 days. The 17-day period was arbitrarily chosen based on the previously published observation that adaptation is associated rapidly with altered floral microorganisms with lactose (8). Secondly, two other studies using naïve probiotics (21,22) showed that bacteria were readily cultured from stool in a short period of time (one week or less). Five subjects consumed 1 g (450×10^9) of the bacteria and the other five consumed 4 g ($4\times450\times10^9$) bacteria. Bacteria were usually mixed with water and taken with meals. The side effects were minor and consisted mainly of nausea, mostly in the high dose group.

The VSL3 probiotic contains four strains of *Lactobacillus* (*L casei*, *L plantarum*, *L acidophilus* and *L bulgaricus*), three of *Bifidobacterium* (*B longum*, *B breve* and *B infantis*), and one strain of *Streptococcus salivarius* subspecies *thermophilus*. The probiotics were a gift of Dr C De Simone (Italy) via Seaford Pharmaceuticals Inc (Ontario). Three random batches were checked for viability by plating the contents of a packet on standard blood agar plates. The microbiological evaluation was carried out in the Mortimer B Davis Jewish General Hospital hospital laboratory under the supervision of Dr M Miller.

Informed consent was obtained from all participants and this study was approved by the Research Ethics Committee of the Sir Mortimer B Davis Jewish General Hospital.

Lactose challenge tests

After a specified supper (with avoidance of lactose gas-forming foods; rice and hamburger were suggested) volunteers were asked to fast (water ad libitum). None of the volunteers took antibiotics, analgesics or any anti- or prokinetic medications. They were asked not to chew gum or smoke but were allowed quiet movement throughout a 4.5 h measurement of exhaled H_2. A 50 g lactose load mixed in water was consumed and after a baseline measurement, breath H_2 was measured every 30 min using a validated handheld H_2 electrochemical sensor (EC60 Vitalograph hydrogen breath monitor, Bedfont Scientific Ltd, United Kingdom) (23,24). The model uses a sealed electrochemical sensor which can detect H_2 in parts per million (ppm) v/v in a range of 0 ppm to 2000 ppm. The average of three exhaled breaths was used at each time interval. Results at each interval were corrected by subtracting the baseline H_2 ppm. In addition, symptoms were recorded by subjects each half hour and graded. The targeted symptoms were bloating, gas, cramps and diarrhea. For each, a score of 1 was assigned for mild (subject aware), 2 for definite presence and 3 for severe symptoms. Although theoretically the maximum score was 108 (9×12 periods) it is virtually impossible to score 12 at each interval. Therefore, for practical purposes, the score system was an open-ended scale. In the case of diarrhea, each loose bowel movement was scored every 30 min. This ordinal scale system was used by the authors previously (12). At the end of 17 days, subjects were asked to repeat the 50 g lactose challenge and record symptoms (test 2).

Statistical analysis

Student's paired *t* tests were used to analyze differences between test 1 and test 2 in both groups. Based on the authors' previous experience of inducing colonic adaptation with lactulose at low dose, it was reasoned that eight to 10 patients per group would suffice to demonstrate a significant difference of a 45% reduction in the sum of breath H_2 on test 2. This difference was chosen because we previously showed (12) that using lactulose as a prebiotic a reduction of 43% between two challenge doses of lactose was statistically significant (12). While this difference may or may not be clinically significant at an individual level for lactose tolerance, it clearly allows demonstration of a population test effect on colonic microbial function. In fact, in our original abstract, six subjects already demonstrated a statistically significant trend at P=0.054 (25). Pearson correlation was used to compare symptoms with sum of breath H_2. Statistical significance was accepted at $P<0.05$.

RESULTS

Four men and six women with a mean age of 38.6±14.6 years (range 24 to 66) undertook the studies. The average baseline H_2 ppm in test 1 was 0.8 ppm (range 0 to 2) in test 1 (n=10) and 4.5 ppm (range 0 to 16) in test 2 (n=10). Changes in Σ4 h breath H_2 and symptom scores for the individuals in group I (one packet/day VSL3) and group II (four packets/day VSL3) are shown in Table 1. Mean ± SD for Σ4 h breath H_2 for test 1 was 279.8±16.4 (CI 256 to 297) for group I, and 323±158.9 (CI 192 to 597) for group II. In test 2 Σ4.5 h breath H_2 for group I was 302±157.8 (CI 152 to 480) and group II 401.0±198.8 (CI 139 to 682). While these differences were statistically insignificant, there was a trend for higher rather than lower Σ4.5 h breath H_2 on test 2 in group II. Similarly, there were no statistically significant changes in symptom score for either group I or group II. While there was a weak significant correlation between global symptom scores for both groups in test 1 (r=0.65), this possible relationship was lost in test 2 (r=0.131). Random cultures of probiotics showed that the ingested products were viable.

DISCUSSION

This small pilot study did not show any benefit for improving lactose intolerance under laboratory conditions. Nevertheless, we felt it is still valuable to report it because of the principle involved in the logic of such studies.

TABLE 1
Demographics and distribution of the Σ of 4.5 h breath hydrogen (BH_2 ppm) and Σ of each 30 min (for 4.5 h) symptom scores (ss) for group I (low dose VSL3) and group II (high dose VSL3)

Patient	Sex	Age	Test 1 BH_2	Test 1 ss	Test 2 BH_2	Test 2 ss
1	F	25	272	16	172	14
2	M	40	282	14	480	35
3	F	45	256	35	245	32
4	M	24	292	63	152	70
5	M	34	297	31	461	6
Mean ± SEM			279.8±7.4	31.8±8.8	302±70.6	31.4±11.1
6	F	53	307	13	429	33
7	F	32	192	25	313	21
8	F	42	274	21	446	29
9	F	61	597	67	682	50
10	M	66	245	10	139	10
Mean ± SEM			323±71	27.2±10.3	401±88.9	28.6±6.6

None of the differences were statistically significant. However, the P value was 0.76 for Σ 4.5 h BH_2 in group I and 0.18 in group II comparing mean BH_2 for test 1 versus test 2, respectively. F Female; M Male

To date, the only successful studies showing improvement of lactose maldigestion with probiotics are those using yogurt (26), other fermented products (27,28) or the addition of live probiotics to milk (29,30). The mechanism in improvement is thought to be due to three factors. First, fermented products contain 30% less lactose. Second, the enzyme β-galactosidase is provided exogenously and continues to digest lactose in the small bowel of LNP subjects. Finally, yogurt may delay gastric emptying and intestinal transit time, thereby reducing the fractional quantity of lactose at the cecum (26). Delayed rate of delivery is putatively associated with reduced symptoms (31,32).

Providing probiotics directly removes the physiological attributes of fermented products. The results obtained here and noted in the literature (21,22) stand in stark contrast to the ability to cause colonic adaptation and improvement in lactose maldigestion with continued lactose consumption (6,7). The process of adaptation with lactose alters fecal flora and favours the emergence of *Lactobacillus* and *Bifidobacteria* species (8).

The specific rationale of using VSL3 is that this probiotic has been successfully used therapeutically in IBD (16-20). In the paradigm of providing naïve probiotics, the following assumptions are made: in lactose maldigesters minimal or zero consumption of lactose may lead to decreased populations of putatively beneficial bacteria; with regular consumption of lactose such bacteria are now numerically expanded and metabolically activated; and if such bacteria (*Lactobacillus* and *Bifidobacteria*) are now given with fermented products or even unfermented milk they may become metabolically activated, facilitating lactose consumption before colonic embedding. If we now wish to establish that unique expansion of an important disease-beneficial bacteria is necessary for enhanced metabolism of lactose on challenge, prestimulation would abrogate such a conclusion. In vitro evidence suggests that infusion of naïve *Lactobacillus* or *Bifidobacteria* aids in consumption of lactose in fecal slurries (9,10). It is not unreasonable to try to reproduce this effect in vivo.

There are indeed few studies that have examined the possible impact of direct probiotics on lactose maldigestion. Hove et al (21) used simultaneous addition of 12 capsules of mixed *Lactobacillus* and *Bifidobacteria* species to a 50 g lactose challenge test. They did not find any improvement in breath H_2 despite previously demonstrating the ability to recover bacteria from stool. More recently, Saltzman et al (22), in a similar elaborate study used a special *L acidophilus* BG2FO4 species (possessing a high β-galactosidase content) which too was cultured from stool after seven days in lactose maldigesters. However, breath H_2 tests at the end did not differ significantly from the beginning, although the sum did increase on the second challenge test (22).

In our own study we also were unable to confirm adaptation by directly providing probiotics. While we were not able to verify colonic bacterial embedding with VSL3 it has been published that such bacteria are cultured from stool after 20 days (33). We feel that some bacterial embedding did occur in the present study because our 17-day adaptation period is close to 20 days and stools were not tested between 10 and 20 days after commencement of feeding, leaving open the possibility of earlier embedding (32). Furthermore, a dose response is suggested to have occurred in the current study because of a noted trend toward increased breath H_2 production with a higher dose of bacteria. This finding was similar to that in the report by Saltzman et al (22).

A longer feeding period and achievement of our intended group sizes may have strengthened our results. It is important to note, however, that the observed trend showed an outcome opposite to what we were expecting. Therefore, achieving a significant difference with the currently observed trend would not have helped our goal. As a result, based on the reports from the literature and this study, we can cautiously conclude that providing metabolically naïve probiotics will not improve lactose maldigestion.

CONCLUSION

This pilot study does not provide a quick link test connecting probiotic-induced colonic adaptation and bacteria proven to be beneficial in therapy of IBD. Despite the limitations of this small pilot study, the results mimic those reported for other efforts to induce improvement in lactose handling by providing naïve probiotics directly. The uniformity of failure suggests that targeted bacteria to date need to be metabolically turned on before demonstrating efficacy. However future studies should include a longer colonic embedding period to determine whether metabolism of lactose might be altered over the extended time.

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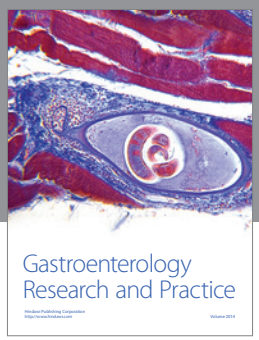

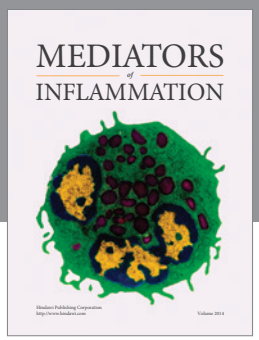

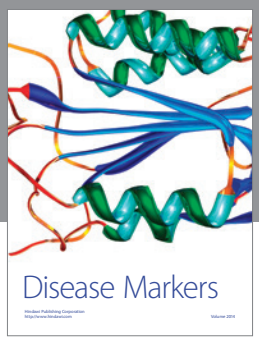

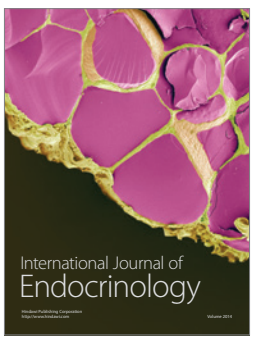

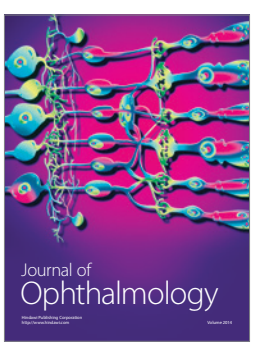

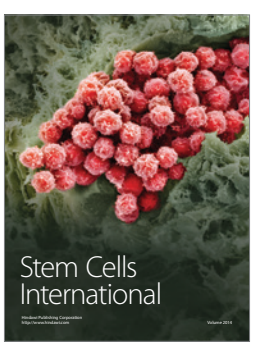

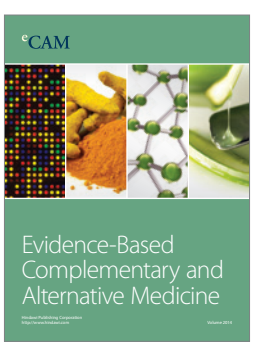

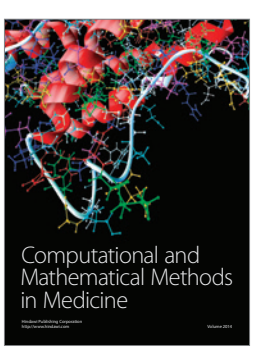

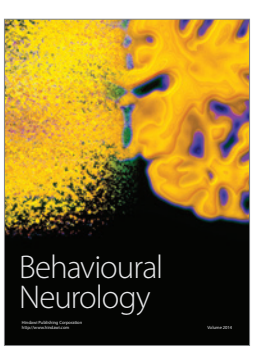

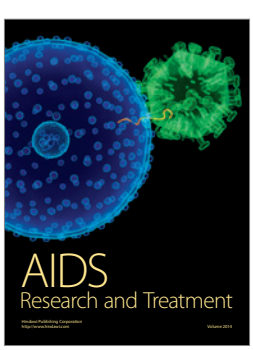

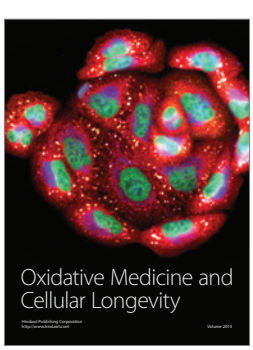

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