Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome, and its relationship with oro-cecal transit time

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Background: Small intestinal bacterial overgrowth (SIBO), which may result from intestinal stasis, is common in malabsorption syndrome (MAS). Quantitative culture of upper gut aspirate is used as a gold standard for the diagnosis of SIBO. Studies on diagnosis of SIBO using non-invasive hydrogen breath tests are contradictory. Methods: 83 patients (age 35 [14-70] y; 50 men) with MAS due to various causes were investigated for SIBO using quantitative culture of upper gut aspirate obtained using a special endoscopic catheter, and glucose and lactulose hydrogen breath tests (GHBT, LHBT). Sustained elevation in breath hydrogen of 12 ppm above basal and two separate peaks (one due to SIBO and the other from colon) were diagnostic of SIBO in GHBT and LHBT, respectively. Oro-cecal transit time (OCTT) was estimated using LHBT in 71 patients. Results: Thirty-two of 81 (39.5%) patients with MAS had SIBO on culture (>10^5 CFU/mL). Using aspirate culture as the gold standard, sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of GHBT to diagnose SIBO were 44%, 80%, 62%, 67% and 65%, respectively; the corresponding values for LHBT were 31%, 86%, 62%, 54% and 55%, respectively. OCTT in patients with SIBO diagnosed on GHBT and/or aspirate culture (n=58) was longer than in those without (170 [60-250] vs. 120 [50-290] min, p=0.02); of others, 7 were hydrogen non-producers and in 6 OCTT could not be assessed due to sustained early peak because of SIBO. Conclusions: GHBT and LHBT are highly specific but insensitive for diagnosis of SIBO in MAS; OCTT is longer in patients with MAS and SIBO than in those without. [Indian J Gastroenterol 2006;25:6-10]

Small intestinal bacterial overgrowth (SIBO) occurs in several diseases of the small bowel1,2 and in healthy elderly persons. Quantitative culture of upper gut aspirate, the gold-standard method for diagnosis of SIBO, is invasive, cumbersome and is not widely available. Therefore, hydrogen breath tests have been used to diagnose SIBO despite discordant data on their sensitivity and specificity. SIBO syndrome is associated with chronic diarrhea and malabsorption of nutrients. Further, various specific diseases causing malabsorption are often associated with secondary overgrowth of bacteria in the small intestine. In health, normal small intestinal motility prevents overgrowth of bacteria; small intestinal stasis as reflected by prolonged oro-cecal transit time (OCTT), therefore, might result in SIBO in patients with chronic diarrhea and malabsorption syndrome (MAS). However, most authors who evaluated SIBO and OCTT in patients with chronic diarrhea and MAS studied these in isolation or used hydrogen breath tests alone for diagnosis of SIBO; the few studies that investigated quantitative culture of small intestinal aspirate included small numbers of patients and did not attempt to evaluate the relationship between bacterial colony counts in the small bowel with OCTT.

We hypothesized that patients with MAS and SIBO would have longer OCTT than those without SIBO as prolongation of OCTT, possibly resulting from the “ileal brake” induced by malabsorbed fat, is believed to be an important factor causing SIBO. We, therefore, undertook a study based on the results of one of our previous studies; in the current study we aimed: (a) to investigate the comparative utility of glucose and lactulose hydrogen breath tests in diagnosing SIBO as compared with the quantitative culture of small bowel aspirate as gold standard, and (b) to evaluate OCTT in patients with MAS with or without SIBO.

Methods

Eighty-three consecutive patients with MAS attending the Luminal Gastroenterology Clinic in our tertiary referral center between July 2000 and December 2003 were studied. All patients had chronic diarrhea and/or other symptoms suggestive of MAS. Causes of MAS, diagnosed using standard criteria, were tropical sprue (n=38), celiac disease (7), panhypogammaglobulinemia (5), giardiasis (6), strongyloidiasis (2), acquired immunodeficiency syndrome (3), intestinal

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tuberculosis (2), Crohn’s disease (1), intestinal lymphangiectasia (1), SIBO with no other cause for MAS (16; most had an underlying disorder that predisposed to SIBO), and unknown (2). None had received antibiotics or drugs influencing gastrointestinal motility within 8 weeks preceding the study. Our institution’s Ethics Committee approved the study.

Diagnosis of MAS and its etiology

The diagnosis of MAS was based on clinical features, documentation of a defect in absorption of two unrelated substances, such as abnormal D-xylose test and abnormal fecal fat value either by van de Kamer’s method or by Sudan staining in most patients,1 or presence of a specific cause for MAS as described by us previously.11 24-h stool collections were weighed for 3 days and average value was taken as stool weight.

Small bowel aspiration and microbiological analysis

Upper small bowel aspirate was collected with sterile precautions during upper gastrointestinal (UGI) endoscopy using a pediatric video colonoscope (in initial 50 patients) or a video gastroscope, and a catheter assembly as described previously.1,2 Aerobic and anaerobic bacterial cultures were done from the aspirate using standard techniques as described previously.1,2 Total bacterial count ≥10^5 colony forming units (CFU) per mL of aspirate was considered diagnostic of SIBO.12

The species of bacteria isolated and their antibiotic sensitivity pattern in 50 of these patients have been reported previously.2

Hydrogen breath tests

Glucose hydrogen breath test (GHBT) and lactulose hydrogen breath test (LHBT) were performed on two separate days, using a breath gas analyzer (Lactoscreen H2 breath tester; Hoek Loos, Amsterdam, Netherlands), as described previously.1 Sustained rise of breath hydrogen (for at least two consecutive readings) by 12 parts per million (ppm) above basal level following glucose administration was taken as evidence of SIBO.1,4 Time interval between lactulose administration and sustained (for at least two consecutive readings) rise of breath hydrogen by 20 ppm above basal level was considered as OCTT.13,14 Two peaks after lactulose administration was considered as evidence of SIBO; in such a situation, the later ‘colonic’ peak (>20 ppm) was used for measurement of OCTT. Measurement of OCTT was considered to have failed if they had a very early sustained peak in breath hydrogen excretion on LHBT in the absence of a later ‘colonic’ peak and had evidence of SIBO by other methods. Average value of basal breath hydrogen >20 ppm despite adequate preparation for breath test on at least two days was considered as high basal breath hydrogen.15

Statistical analysis

Categorical and continuous variables were compared using chi-squared test with Yates’ correction (EpiInfo; CDC, Atlanta, USA) and Mann-Whitney U test (SPSS, version 10), respectively. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated using standard formulae.

Results

All patients (age 14-70 [mean 35] y; 50 men) presented with chronic small bowel diarrhea, except one who presented with severe anemia and malnutrition. D-xylose was abnormal (<1 g/5 g/5 h; 0.45 [0.1-1.8] g D-xylose was excreted in the urine) in 79 of 83 patients. In the remaining 4 patients, fecal fat was abnormal (>7 g/24 h) in three and the other had intestinal lymphangiectasia on endoscopic duodenal biopsy. Median and range of fecal weight, number of fat droplets on Sudan III-stained spot stool specimen, and quantitative fecal fat using van de Kamer’s method were 496 (175-3050) g/day, 16 (3-100)/high power field and 7.8 (3.8-20) g/day, respectively. Of the 81 patients with MAS in whom upper gut aspirate could be obtained, 32 (39.5%) had colony counts diagnostic of SIBO.

Utility of hydrogen breath tests for diagnosis of SIBO

GHBT was done in 75 patients. In two of them, upper gut aspirate could not be obtained. GHBT was positive in 20 (including 5 with high basal level), negative in 29 and indeterminate in 24 (7 hydrogen non-producers and 17 with high basal breath hydrogen and insignificant elevation after glucose ingestion). Upper gut aspirate could not be obtained in two of 71 patients who underwent LHBT. LHBT showed two separate peaks diagnostic of SIBO in 13, was negative for SIBO in 38, and indeterminate in 18 (7 hydrogen non-producers and 11 with high basal breath hydrogen level). Performance of GHBT and LHBT for SIBO, as compared to aspirate culture, is shown in the Table.

OCTT and its relationship with bacterial colony counts in gut aspirate

LHBT was performed in 71 patients. Seven (8.4%) of them were hydrogen non-producers (in two of
Table: Hydrogen breath tests as compared with upper gut aspirate culture in diagnosis of small intestinal bacterial overgrowth in patients with malabsorption syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GHBT</th>
<th>LHBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIBO (≥10^5/mL) on culture</td>
<td>Pos*</td>
<td>Neg**</td>
</tr>
<tr>
<td>Pos#</td>
<td>Neg**</td>
<td></td>
</tr>
<tr>
<td>No SIBO on culture</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>80</td>
<td>86</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>62</td>
<td>61.5</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>67</td>
<td>54</td>
</tr>
<tr>
<td>Diagnostic accuracy (%)</td>
<td>65</td>
<td>55</td>
</tr>
</tbody>
</table>

Pos - Positive; Neg - Negative.
*Five of them also had high basal breath hydrogen level
**Those with indeterminate test result due to hydrogen non-producing state or due to high basal breath hydrogen level without rise by 12 ppm above basal were considered negative
#None of these patients had high basal breath hydrogen level

whom aspirate could not be obtained). Six of the 64 patients with interpretable LHBT had a sustained early peak followed by plateau in breath hydrogen level soon after ingestion of lactulose (after 30 min in 4, 40 min and 60 min in one each). Five of them had SIBO as documented by GHBT and/or quantitative small bowel aspirate culture, and in one there was high basal breath hydrogen level though culture failed to show SIBO. It was thought that OCTT was unlikely to be so short as such early peak might have resulted from bacterial overgrowth in the small bowel. None of these patients had two separate peaks to estimate OCTT using the later peak; hence, it was assumed OCTT could not be estimated in them. Therefore, OCTT was available in 58 patients. OCTT could be estimated in all 11 patients with high basal breath hydrogen as hydrogen level rose >20 ppm above basal after lactulose ingestion in all of them.

OCTT was longer in patients with aspirate colony count ≥10^5 CFU/mL than in those without (165 [range 60-250] vs. 120 [50-290] min, p=0.04). OCTT in patients with SIBO diagnosed on GHBT and/or aspirate culture (n=58) was longer than in those without (170 [60-250] vs. 120 [50-290] min, p=0.02).

Discussion

This study shows that GHBT and LHBT are specific but insensitive for the diagnosis of SIBO in patients with MAS, and that OCTT is longer in patients with SIBO.

We have previously shown that patients with MAS due to various causes often have SIBO; this might have clinical significance in causing unresponsiveness of celiac disease to gluten-free diet. We have proposed that small bowel stasis, as evidenced by prolonged OCTT, might be a factor responsible for SIBO in patients with tropical sprue, a common cause of sporadic MAS in northern Indian adults and in other developing countries. Similar mechanisms might operate in MAS due to other causes, as prolongation of OCTT or whole gut transit has also been reported in other diseases like celiac disease, Crohn’s disease and strongyloidiasis. Such prolongation in OCTT might result from the “ileal brake” induced by malabsorbed fat passing through the ileum, as suggested in patients with MAS due to tropical sprue or due to neuromyopathy of gut muscles.

If prolonged OCTT is an important factor causing SIBO in patients with MAS, one would expect a significant difference in OCTT in patients with SIBO than in those without it. However, no previous study addressed this issue. This is perhaps the first study that shows that patients with MAS and SIBO have longer OCTT than patients without SIBO.

What could influence the development of SIBO in patients with MAS? The small intestine in patients with MAS is often dilated and contains excessive fluid and nutrients. A proportion of patients had high basal breath hydrogen level though culture failed to show SIBO. It was thought that OCTT was unlikely to be so short as such early peak might have resulted from bacterial overgrowth in the small bowel. None of these patients had two separate peaks to estimate OCTT using the later peak; hence, it was assumed OCTT could not be estimated in them. Therefore, OCTT was available in 58 patients. OCTT could be estimated in all 11 patients with high basal breath hydrogen as hydrogen level rose >20 ppm above basal after lactulose ingestion in all of them.

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This might result from bacterial flora in the small bowel acting on the previous meal or normal colonic flora fermenting unabsorbed carbohydrates; such a problem is not unexpected in patients with markedly prolonged gut transit time.

Some authors considered high basal levels of breath hydrogen as evidence of SIBO; however, such criteria would compromise the specificity of hydrogen breath test as fasting breath hydrogen may be high due to action of oral bacterial flora on test sugars despite oral cleansing with chlorhexidine. Therefore, we did not diagnose SIBO based only on high fasting breath hydrogen levels. This view is supported by previous studies that showed highest specificity of diagnosis of SIBO when rise in breath hydrogen following ingestion of test sugars is combined with high basal breath hydrogen levels.

Hydrogen breath test was positive in a proportion of patients in whom microbiological analysis of upper gut aspirate failed to show SIBO. A possibility of false negative result in microbiological analysis is unlikely though it has been reported in an occasional study particularly when fluid from a single site of the intestine was cultured. The frequency of positive result with culture in our study far exceeded that with hydrogen breath test, despite special precautions while designing the catheter for aspiration, and during its sterilization, endoscopic procedure and processing of specimens. Therefore, the patients who had positive hydrogen breath test in absence of microbiological evidence of SIBO likely represent false positive hydrogen breath test.

This is difficult to explain as glucose is unlikely to pass to a colon colonized heavily with bacteria without being absorbed in the small bowel, though an occasional study did report such a phenomenon. Our data showing low sensitivity and high specificity of hydrogen breath test is in accordance with most previous studies.

Glucose hydrogen breath test had a marginally higher sensitivity than LHBT. Glucose is readily absorbed in the small bowel and cannot reach the colon; this is its main advantage for diagnosis of SIBO. That any peak is abnormal is the main advantage in terms of the interpretation of tests using glucose over those using nonabsorbable substrates such as lactulose. Further, bacteria in patients with SIBO usually come from the colon. Therefore, colony counts of bacteria increase progressively in the distal small bowel. Hence, breath hydrogen progressively increases as the lactulose travels down the small bowel. Therefore, there may not be a drop in the hydrogen level before it rises again after lactulose reaches the cecum. This makes the LHBT less sensitive for the diagnosis of SIBO as the classical double peaks are rarely obtained.

In conclusion, we found that GHBT and LHBT are highly specific but quite insensitive for diagnosis of SIBO in patients with MAS, and that OCTT is longer in patients with SIBO than in those without.

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