Original Article

Comparison of Abnormal Hydrogen Production Between Simultaneous Lactulose and Glucose Hydrogen Breath Test with Small Bowel Scintigraphy

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ABSTRACT

Background: Glucose and lactulose hydrogen breath tests have been advocated as indirect methods for identifying patients with small bowel bacterial overgrowth. It is controversy regarding which substrate is better.

Aim: To compare the ability of glucose and lactulose H_2 breath test for identifying abnormal H2 production in the small bowel.

Patients and Methods: Forty-one patients who were suspected of having small bowel bacterial overgrowth underwent 2 H_2 hydrogen breath tests with 50 gm glucose or 10 gm lactulose orally, in random orders, 7 days apart. The glucose or lactulose solution was labeled with 99mTc. A breath sample was obtained at baseline. Then scintigraphic images and breath samples were obtained at time 0 and every 15 min after ingestion of the glucose or lactulose until the radioactive substances reach the cecum. Positive H_2 breath test was defined as an increase of H_2 10 ppm above baseline before the radioactive substances reach the cecum. Orocecal transit time was the time spent for the radioactive substance to travel from oral cavity to cecum.

Results: All patients completed both breath test studies. Orocecal transit time for glucose was 191 ± 15 min, significantly longer than lactulose (62 ± 5 min, $p < 0.001$). Ten and 4 patients had positive glucose and lactulose H_2 breath test respectively ($p = 0.15$). One patient had positive of both H_2 breath tests. Thirteen patients with positive glucose and lactulose breath test had increase H_2 production begin in the first half of the orocecal transit time, no patient with glucose breath test had positive test begin in the second half of the orocecal transit time. One patient had positive lactulose hydrogen breath test at distal half of small bowel. Patients who had positive at least one breath test had significant longer orocecal transit time of glucose (259.5 ± 16.3 min) and lactulose (105 ± 6.9 min) compared to patients who had negative results of both breath tests. (169.4 ± 13.6 min and 57.2 ± 4.7 min, for glucose and lactulose, respectively, $p < 0.05$)

Conclusions: Glucose H_2 breath test trends to be more sensitive than lactulose breath test for detection of abnormal H_2 production in the small bowel. However, 50 gm glucose breath test could not detect abnormal H_2 production in the distal half of the small bowel. Although lactulose breath test could detect abnormal H_2 production in the distal small bowel, it could not identify most patients with positive glucose breath test, supporting the hypothesis that lactulose may not be fermented by gut flora in some patients.

Key words : Lactulose, Glucose hydrogen breath test, Small bowel scintigraphy

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Background

Small bowel bacterial overgrowth is a condition that normal bacterial flora has increased in number more than the usual amount. Many gastrointestinal problems are the result of this condition such as chronic abdominal pain, abdominal bloating, chronic diarrhea and including symptoms and sign of vitamin B12 deficiency. By definition we can make a diagnosis of small bowel bacterial overgrowth when the jejunal fluid culture show bacterial colony count more than 10^5 colony forming unit (CFU)/ml.[1] The methods to obtain the jejunal fluid by using endoscopy or jejunal intubation under fluoroscopy are invasive and troublesome although they are the gold standard.[2,3] The other drawbacks of these ways are they can give either a false positive and false negative results due to oral bacterial contamination[4] and random error[5], respectively. Practically, we prefer noninvasive mean, a hydrogen breath test. The rationale of this test is to detect hydrogen gas which is produced by small bowel bacterial metabolism after taking the substrate sugar. There were many studies trying to compare the sensitivity between glucose and lactulose but no meta-analysis that makes a conclusion. Up to now, it is still controversy whether which substrate is better between glucose and lactulose. There is a study showed that small bowel scintigraphy can enhanced the interpretation of hydrogen breath test in term of increasing in sensitivity and specificity (16.7% vs 38.9% and 70% vs 100% respectively).[6] By using this method doing concomitantly, hydrogen breath test can be more accurate.

The aim of this study was to compare the ability of glucose and lactulose hydrogen breath tests for identifying abnormal hydrogen production in the small bowel when were interpreted simultaneously with small bowel scintigraphy.

Patients and Methods

A prospective analytic study was undertaken to compare the result of glucose and lactulose hydrogen breath tests which were done simultaneously with small bowel scintigraphy. Target population are the patients who have symptoms and/or predisposing conditions suggesting of small bowel bacterial overgrowth who have visited King Chulalongkorn Memorial Hospital. Inclusion criteria are patients age between 17-80 years old and presented with chronic abdominal pain, abdominal bloating or chronic diarrhea. Patients might have underlying conditions which predisposed to cause small bowel bacterial overgrowth, for instance diabetes mellitus, scleroderma, intestinal pseudo-obstruction, previous gastrointestinal surgery, inflammatory bowel disease, small bowel diverticula, or have been taking acid reducing agent for a long period of time. Patients were excluded from the study if they were pregnant, did take antibiotic during last four weeks, and was put on the medications (such as tricyclic antidepressant, calcium channel blockers, prokinetic and macrolide antibiotics) known to affect gastrointestinal motility and could not be discontinued for at least 7 days before studies

All patients underwent two hydrogen breath tests with simultaneous small bowel scintigraphy studies in random order, 7 days apart. Patients were informed to avoid incompletely absorbed carbohydrates such as corn, pasta and bread on the day before study and avoid smoking and exercise on the study day. Every patient had to fast after midnight and using oral antiseptic solution immediately before the study started. Glucose 50 gram or lactulose 10 gram plus 500 MBq of 99-Tcm phytate in 100 cc of water was administered. Imaging were carried out using gamma camera every 15 minutes until the substrate reached the cecum. A breath sample was collected at baseline and before each scintigraphic imaging. Breath samples were analyzed by Quintron Microlyser and were interpreted with orocecal transit time. An increased in hydrogen concentration at least 10 part per million (ppm) from baseline at the time which orocecal transit study determined that the radioactive substance was located in the small bowel was considered positive.

The data was analyzed by SPSS for window (version 11.2, Chicago, IL). The student's t test, McNemar chi-square test, chi-square test and logistic regression were used for statistical analysis. Data were expressed as mean ± SD or mean ± SEM as appropriated. $p < 0.05$ was considered statistical significance.

Results

Forty-one patients have completed both breath test studies. There were 12 male (29.3%) and 29 female (70.7%) with mean age of 50 ± 13 years old. The mean duration of symptoms was 30 months. The most common presenting symptoms was abdominal bloating 92.7% . Some patients have underlying predisposing condition, which were gastroesophageal reflux disease (31,7%), scleroderma (19.5%), diabetes mellitus (19.5%) and small bowel diverticulum (2.4%). Four patients (9%) had undergone previous Billroth II gastrojejunostomy and more than half of patients (56.1%) have been taking acid reducing medication. Patients baseline characteristics are shown in Table 1.

Orocecal transit time for glucose was 191 ± 15 min, significantly longer than lactulose (62 ± 5 min, $p < 0.001$). Ten and 4 patients had positive glucose and lactulose H_2 breath test respectively ($p = 0.15$) as shown in Figure 1.

One patient had positive of both H_2 breath tests. Thirteen patients with positive glucose and lactulose breath test had increase H_2 production begin in the first half of the orocecal transit time, no patient with glucose breath test had positive test begin in the second half of the orocecal transit time. One patient with lactulose breath had increased hydrogen production in the distal half of the small intestine. Patients who had positive at least one breath test had significant longer orocecal transit time of glucose (259.5 ± 16.3 min) and lactulose (105 ± 6.9 min) compared to patients who had negative results of both breath tests. (169.4 ± 13.6 min and 57.2 ± 4.7 min, for glucose and lactulose, respectively, $p < 0.05$)

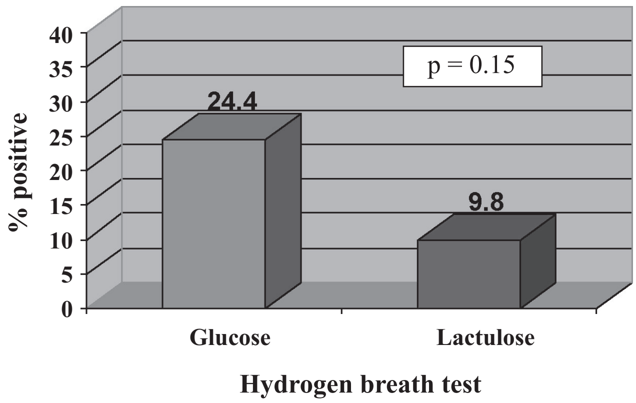

Figure 1 The result of glucose and lactulose hydrogen breath tests.

Table 1 Baseline characteristics of 41 patients.

Baseline characteristics	N (%)
Gender (male)	12 (29.3)
(female)	29 (70.7)
Duration of symptoms	30.5 ± 32.9
Presenting symptoms	
Abdominal pain	20 (48.8)
Abdominal pain relief after defecation	18 (43.9)
Abdominal bloating	38 (92.7)
Flatus	26 (63.4)
Constipation	16 (39)
Diarrhea	21 (51.2)
Loose stool	27 (65.9)
Hard stool	13 (31.7)
Urgency	7 (17.7)
Tenesmus	26 (63.4)
Early satiety	22 (53.7)
Prolonged fullness	19 (46.3)
Abdominal distention	32 (78)
Underlying diseases	
DM	8 (19.5)
Scleroderma	8 (19.5)
Small bowel diverticulum	1 (2.4)
GERD	13 (31.7)
History of taking acid reducing agents	23 (56.1)
Previous gastrointestinal surgery	9 (23.1)
B II gastrojejunostomy	4 (9)
Appendectomy	4 (9)

There was no correlation between patient's presenting symptoms and the results of hydrogen breath test analyzed by multivariate analysis ($p > 0.05$).

Few patients had minor gastrointestinal side effects after taking glucose or lactulose while they were testing. Adverse reactions are abdominal bloating, abdominal pain, diarrhea, flatus and belching which were found less than 13% for each symptom in both study groups. There was no significantly difference in side effects between both groups also.

DISCUSSION

This study showed that there was a higer positive results by glucose than lactulose hydrogen breath test when interpreted simultaneously with small bowel scintigraphy for identifying patients with small bowel bacterial overgrowth, although it was no statistical significance. There is hypothesis that glucose suppose to be the better substrate due to firstly, almost all bacterial flora can ferment glucose; and secondly, it is easily absorbed in the small intestine makes it unlikely to give a false positive result by colonic bacterial fermentation. In contrary, lactulose causes shorten small intestinal transit time[7] and the transit time of lactulose was affected by the phases of migratory motor complex (MMC)[8]. These effects cause the false positive result from early colonic bacterial fermentation by rapid transit induced by phase III MMC. The other disadvantage of using lactulose as a substrate of the hydrogen breath test is that 25-40% of bacteria in some group of patient has no enzyme that can ferment lactulose.[9] From our study, the result of orocecal transit time obviously revealed that glucose yielded a longer orocecal transit time than lactulose. (191 ± 15 min vs 62 ± 5 min, p <0.001) This confirmed previous study that lactulose decrease orocecal transit time. Moreover, it showed that glucose causes prolongation of small bowel transit time.

Our data showed that patients who had positive at least one breath test had significantly longer orocecal transit time of glucose and lactulose compared to patients who had negative results of both breath tests. This result imply that the longer transit time may associate with small bowel bacterial overgrowth and positive hydrogen breath test.

All positive results of glucose hydrogen breath test occurred in first half of orocecal transit time confirmed that glucose was totally absorbed before reaching the cecum. By the way, this can cause false negative result because it could not detect small bowel bacterial overgrowth in the distal part of small intestine. As seen in this study that glucose hydrogen breath test could not identified three patients with small bowel bacterial overgrowth while lactulose hydrogen breath test can.

In this study, although glucose hydrogen breath test yielded more frequent positive results compared with lactulose hydrogen breath test, there was no significant difference. This may explain by 1) the low prevalence of abnormal hydrogen breath test in selected population, which may caused type I error and 2) the hydrogen breath test itself may have a low sensitivity and 3) the last reason is a limitation of the test that could not be applied on some people who has bacteria which cannot produce hydrogen gas, but do give other gas such as methane instead and this is found in 15-20% of general population.[10] Previous study showed that higher dose of glucose gave more positive results than lower dose. It is possible that increasing the dose of glucose from 50 gram to 80 gram might enhance the positive rate and delineate the difference.

Though, there was no significant difference in side effect between testing by glucose and lactulose, diarrhea happened in five patients on the day that they took lactulose while no one has diarrhea when glucose was administered. This might worsen symptom of patients who already have diarrhea so it should be avoided in this group of patients.

In conclusion, glucose H_2 breath test trends to be more sensitive than lactulose breath test for detection of abnormal H_2 production in the small bowel. Theirs results might light up the idea of combining both substrate for hydrogen breath test which suppose to increase the yield of positive result.

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