

INTRODUCTION

❖ Irritable Bowel Syndrome (IBS) is a common gastrointestinal ailment that is defined by the Rome I classification as recurrent abdominal pain at least 3 days per month, with at least two of the following:

- improvement on defecation
- onset associated with a change in stool frequency
- onset associated with a change in stool form¹

❖ Recently, small intestinal bacterial overgrowth (SIBO) has been implicated in the pathogenesis of this disorder, with numerous studies demonstrating excessive endogenous bacteria within the small intestine in IBS patients as measured by lactulose breath tests (LBT).²

❖ Controversy has arisen with regards to the effect that concurrent proton-pump inhibitor (PPI) usage may have on these breath tests.

- Many studies suggest a clear overlap between IBS and gastroesophageal reflux disease (GERD), and thus it is postulated that PPI usage may promote SIBO, which would consequently cause false-positive LBT results in IBS patients.³

❖ We sought to explore this postulation in our study, as well as elucidate any other effects that PPI-usage may have on LBT results.

METHODS

Patient Population

Subjects referred to a tertiary care medical center for a lactulose breath test were prospectively recruited to participate. Patients were eligible if they met Rome I criteria for IBS and excluded if they had a history of inflammatory bowel disease, intestinal resection, thyroid disease, diabetes or chronic narcotic medication use.

Primary Study Design

Prior to conducting the breath tests, subjects were given a questionnaire that included symptoms, past medical history, current medication use, and demographic information. Once completed, a baseline breath sample was obtained followed by ingestion of 10 g of lactulose with 1-2 ounces of water. Breath samples were then collected at 15-min intervals for 180 minutes. End expiratory breath samples were taken to ensure alveolar gas sampling. Samples were analyzed for hydrogen, methane, and carbon dioxide reported in parts per million (ppm), using a Model SC, Quintron gas chromatograph. Measurements were plotted graphically.

Breath Test Analysis

The breath tests were analyzed comprehensively so as to evaluate for any possible effects of the PPI, not just the positivity of the breath test. Other factors that were measured were the time to first and second hydrogen peaks, and the amplitude of those peaks. A test was considered positive if there was a rise in breath hydrogen gas ≥ 20 ppm above baseline at or before 90 minutes from start.

Statistical Analysis

The number of (+) LBTs in PPI users was compared with the number of (+) LBTs in non-PPI users using a chi-square test expressed as an odds ratio and confidence interval. To compare the difference in mean values for the various qualities of the breath test results between the two groups, a Wilcoxon rank sum analysis was conducted.

DATA

Figure 1: Anatomy and analysis of the lactulose breath test.

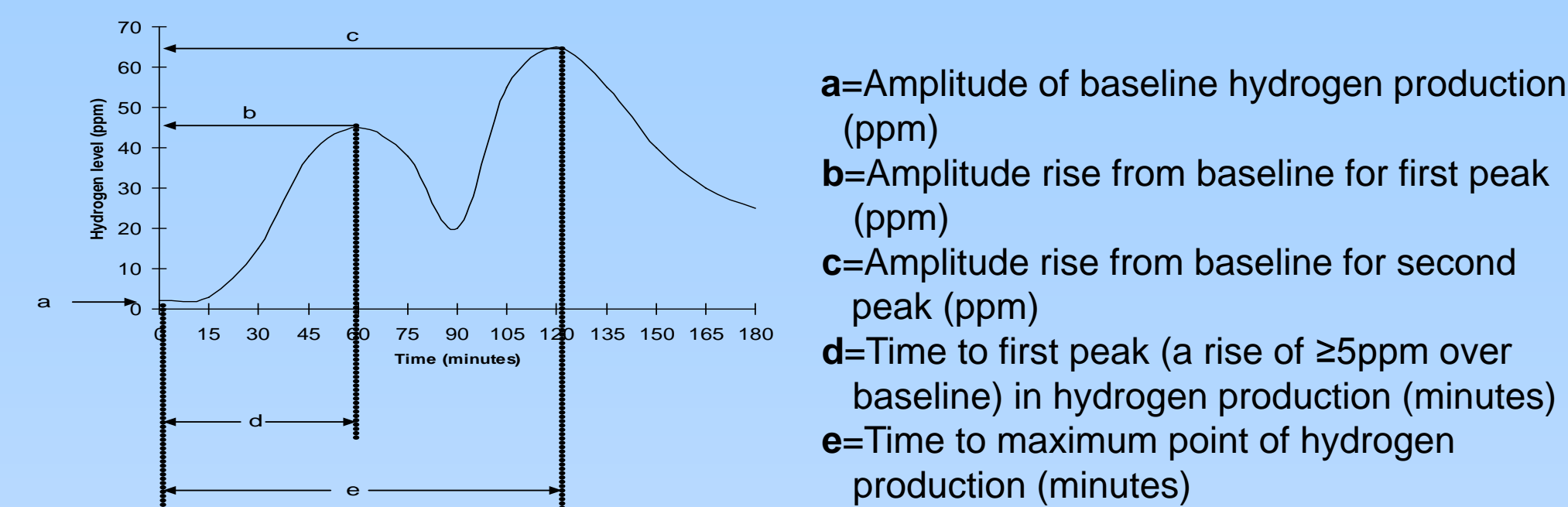


Figure 2: Comparison of methane producers between PPI users and non-PPI users

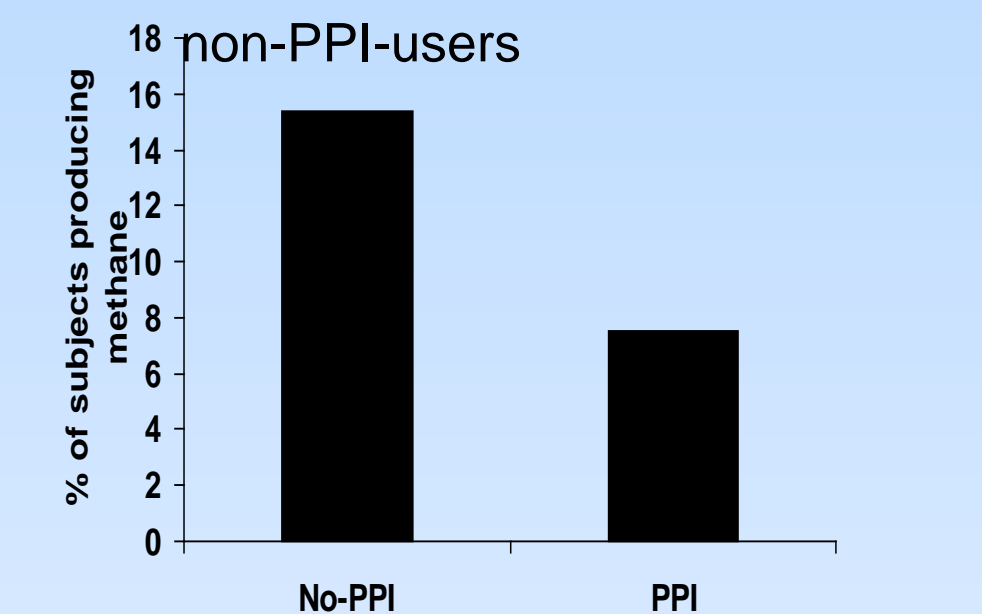


Table 1: Subject demographics

	Non-PPI Use (%) (N=449)	PPI Usage (%) (N=106)	p-value
Gender			
Male	98 (21.8)	28 (26.4)	0.31
Female	351 (78.2)	78 (73.6)	
Mean Age (years)	43.1 \pm 15.8	46.1 \pm 16.0	0.069

Table 2: Effect of PPI use on the proportion of subjects with SIBO and amplitude of hydrogen production

Parameter		Non-PPI	PPI	P-value
$\Delta 20$ ppm by 90 minutes [¶]	n (%)	253 (56.3)	49 (46.2)	0.07
	Mean amplitude	45.5 \pm 27.0	53.0 \pm 38.5	0.20
≥ 20 ppm by 90 minutes [‡]	n (%)	281 (62.6)	64 (60.4)	0.74
	Mean amplitude	49.9 \pm 28.6	51.6 \pm 38.5	0.73
≥ 20 ppm any time*	n (%)	349 (77.7)	88 (83.0)	0.29
	Mean amplitude	61.2 \pm 34.2	59.8 \pm 43.3	0.77

[¶]Subjects with ≥ 20 ppm rise in hydrogen production over baseline.

[‡]Subjects with any value of ≥ 20 ppm before 90 minutes.

*Subjects with hydrogen levels ≥ 20 ppm at any point during the 180 minute test.

Table 3: Comparison of breath test parameters from Figure 1 based on use of acid-suppressive therapy

Breath Test Parameter	PPI Users (n=449)	Non-PPI Users (n=106)	P-value
a. Baseline breath H ₂	6.52 \pm 6.39	6.41 \pm 7.52	0.88
b. Measure 3 in all patients	27.5 \pm 29.1	28.0 \pm 35.3	0.89
c. Amplitude of 2 nd H ₂ peak (ppm)	49.3 \pm 37.6	48.5 \pm 43.8	0.87
d. Time to 1st H ₂ peak (min)*	56.4 \pm 23.0	58.2 \pm 26.1	0.58
e. Time to maximum rise in H ₂ (min) [¶]	99.1 \pm 28.4	95.8 \pm 27.6	0.29

*Only among subjects with a rise of greater than 5 ppm above baseline ≤ 90 minutes (n=313 in non-PPI and 76 in PPI users).

[¶]Only in subjects with a detectable peak (n=406 for non-PPI and 98 for PPI users).

H₂ = hydrogen.

ppm = parts per million

DISCUSSION

❖ In this study we demonstrate that there is no statistically significant difference between prevalence of a hydrogen positive LBT in IBS patients who report taking a PPI and those not taking one.

❖ Though not significant, there is a lower prevalence of positive LBTs among IBS patients using PPI therapy (46.2%) compared to those not on PPI (56.3%)

❖ After an extensive analysis of the breath tests (Figure 1), there is also no change in any of the dynamics of hydrogen production between those using and not using PPI (Table 2 and Table 3)

❖ There is an association between the use of PPI and the presence or absence of methane on the breath test. (Figure 2)

In the last decade, there has been a growing interest in the role of gut bacteria in the pathophysiology of IBS. Though there is no gold standard test for the diagnosis of SIBO, numerous studies examining the link between SIBO and IBS have been conducted using breath testing; nearly all of the studies which use age and sex-matched controls demonstrate a significant difference between IBS subjects and controls.⁴ Further indirect evidence for a gut flora problem in IBS is data suggesting that IBS subjects respond to antibiotics.⁵

It has been suggested that PPIs, by increasing stomach pH, can precipitate an increase in foregut contamination, which may lead to the symptoms of IBS. In the case of bacterial overgrowth, however, a recent review of the literature suggests that although PPIs may affect the bacterial population, there is only rarely a clinical change.⁶ Also, in the case of SIBO in IBS, the hypothesis is that of coliform excess in the full 15 feet of small intestine. This is in contrast to the 8-12 inches of foregut that may be affected by PPI therapy.⁷ A final question begs an answer: how long do bacteria need to be exposed to acid in order to curb their number? After 24 hours following a PPI dose, acid production has likely broken through.⁸

Previous smaller studies have demonstrated that PPIs do not seem to affect the lactulose breath test. In the current study we confirm this finding. We also note the higher prevalence of methane production among IBS subjects not taking PPI. While it is known that methane on breath testing is associated with constipation-predominant IBS⁹, and that methane may have physiologic effects on transit, the methane association with lack of PPI cannot be easily explained.¹⁰

REFERENCES

1. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006; 130: 1480-91.
2. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastro* 2000;95:3503-6.
3. Nastaskin I, Mehdiqhani E, Conklin J, et al. Studying the overlap between IBS and GERD: A systematic review of the literature. *Dig Dis Sci* 2006;51:2113-20.
4. 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*. 2003;98:412-9.
5. Pimentel M, Park S, Mirocha J, et al. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006;145:557-663.
6. Williams C, McCall KEL. Review article: proton pump inhibitors and bacterial overgrowth. *Aliment Pharmacol Ther* 2006;23:3-10.
7. Rubinstein E, Mark Z, Haspel J, et al. Antibacterial activity of the pancreatic fluid. *Gastroenterol* 1985;88:927-32.
8. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease – where next? *Aliment Pharmacol Ther* 2005;22:79-94.
9. Pimentel M, Mayer AG, Park S, et al. Methane production during lactulose breath test is associated with gastrointestinal disease presentation. *Dig Dis Sci* 2003;48:86-92.
10. Pimentel M, Lin HC, Enayati P, et al. Methane, a gas produced by enteric bacteria, slows intestinal transit and augments ileal contractile activity. *Am J Physiol Gastrointestinal Liver Physiol* 2006;290:G1089-95.