Original Article

Phloroglucinol in Irritable Bowel Syndrome

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Abstract

Objective: To determine the efficacy and tolerability of phloroglucinol, an antispasmodic agent in the treatment of Irritable Bowel Syndrome (IBS).

Methods: It was an open label (quasi interventional) study. One hundred patients coming to the gastroenterology clinics of Aga Khan University Hospital with IBS as defined by the Rome II criteria were enrolled between February 2004 and September 2004 to participate in the trial and were treated as outpatients. Phloroglucinol (Himont) 50mg orally three times daily was given for two months. Symptoms were assessed before and during treatment using a questionnaire.

Results: One hundred patients were enrolled in the study. Of them 61% (61/100) were males and 39% (39/100) were females. Their mean age was 41±14 years. Sixty-eight patients completed the study and 28 dropped out. On Phloroglucinol treatment there was an overall statistically significant improvement in abdominal pain ($p<0.001$), frequency of stools per day ($p<0.001$), urgency ($p<0.001$), passage of mucus per rectum ($p<0.001$), sense of incomplete defecation ($p=0.001$) and bloating ($p=0.001$). However, no response was seen in the feature of straining in both genders ($p=0.676$). The difference in response to treatment according to gender separately showed statistically significant improvement in the sense of incomplete defecation in females alone ($p=0.003$).

Conclusion: Phloroglucinol in a dose of 50mg three times daily is effective and well tolerated by the IBS patients. It relieves most of the symptoms of IBS (JPMA 56:5;2006).

Table 1. The criteria used for the diagnosis of irritable bowel syndrome.

Rome II Symptom Criteria for IBS

At least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

1) Relieved with defecation

2) Onset associated with a change in frequency of stool

3) Onset associated with a change in form (appearance) of stool.

Other symptoms that are not essential but support the diagnosis of IBS:

(a) Abnormal stool frequency (greater than 3 bowel movements/day or less than 3 bowel movements/week); (b) Abnormal stool form (lumpy/hard or loose/watery stool); (c) Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); (c) Passage of mucus (d) Bloating or feeling of abdominal distension

Introduction

Irritable bowel syndrome (IBS) is a common disorder which is associated with abdominal pain, bloating and bowel habit changes characterized by loose bowels, constipation or an alteration between these extremes.[1] The current consensus "Rome II criteria' define IBS as a group of functional bowel disorders with two common prominent clinical features, abdominal pain or discomfort or pain that is associated with change in bowel habit and disordered defecation.[2] The disorder affects approximately 15%-20% of the world population and is also common in Asian countries such as China, India, Japan and Pakistan.[3-6] Although many IBS sufferers do not seek medical care, IBS has been estimated to account for 20% - 50% referrals to gastroenterology clinics.[7]

The etiology and pathophysiology of IBS is multifactorial and no proven single etiology or effective treatment has emerged. Possible abnormalities in the processing of sensory stimuli in the "brain-gut" axis leads to the visceral hypersensitivity and secondary motility change. In some patients, a multi-factorial mechanism including stressful life events or other psychological factors contribute considerably.[8-10] Among intestinal pathogens Blastocystis hominis (B. hominis) is a unicellular protozoan found in the large intestine of humans. Infection occurs worldwide but is commonly found in the tropics and developing countries.[11] The pathogenic potential of B. hominis in the human intestine is controversial because the organism has been found in both symptomatic and asymptomatic individuals. Currently, there is no single therapeutic modality of proven benefit in all IBS patients and treatment is tailored to relief of predominant symptom.[12] Spasmolytics are frequently effective in relieving pain in patients with IBS.[13] Among them phloroglucinol has been used for many years and has proven effective.[14] It was shown to provide relief to abdominal cramps together with a significant reduction in the number and amplitude of phasic contractions by acting directly on the colonic smooth muscle.[15] This study was designed to test the efficacy and tolerability of Phloroglucinol in the treatment of IBS. It relieves pain and is considered to be free of anticholinergic side effects. No toxicity has been observed even at high doses and there is remarkable activity against pain.

Patients and Methods

It was an open label (quasi-interventional) study investigating the effect of Phloroglucinol (Himont) 50mg orally three times daily for two months. It was preceded by a two weeks baseline period with no medication. One hundred patients coming to the gastroenterology clinics of Aga Khan University Hospital with IBS as defined by the Rome II criteria (Table 1) were enrolled to participate in the trial and were treated as outpatients. The study was approved by the ethic review committee of the hospital. Those consenting to participate were given the trial drug treatment. Exclusion criteria were defined as all patients with colonic disease with active parasitic infestation, inflammatory

Table 2. Gastrointestinal symptoms on treatment with Phloroglucinol.

	Base line (n=68)	At 8th week end of treatment (n=68)	Difference	95% C.I. for Difference	P-value†
Abdominal Pain	65 (96%)	20 (29%)	67%	53 - 69%	< 0.001
Frequency of stool (≥3 per day)	39 (57%)	9 (13%)	44%	32 - 47%	< 0.001
Straining	30 (44%)	27 (40%)	4%	0 - 18%	0.676
Urgency	51 (75%)	23 (34%)	41%	26 - 48%	< 0.001
Sense of incomplete defecation	51 (75%)	33 (48%)	26%	12 - 35%	0.001
Mucus	34 (50%)	8 (12%)	38%	23 - 45%	< 0.001
Bloating	48 (71%)	29 (43%)	28%	12 - 37%	0.001

Results are expressed as percentages, Difference of percentage and 95% Confidence Interval for difference of percentage, †p-value has been calculated through McNemar Test.

Table 3. Gastrointestinal symptoms in male patients on treatment with Spasfon.

	Base line (n=40)	At 8th week end of treatment (n=40)	Difference	95% C.I for Difference	P-value†
Abdominal Pain	38 (95%)	12 (30%)	65%	44 - 69%	< 0.001
Frequency of stool (≥3 per day)	23 (57%)	8 (20%)	37%	18 - 42%	0.007
Straining	18 (45%)	18 (45%)	0%	-	0.789
Urgency	29 (72%)	17 (42%)	30%	8 - 42%	0.009
Sense of incomplete defecation	27 (67%)	20 (50%)	17%	0 - 31%	0.121
Mucus	24 (60%)	7 (17%)	42%	20 - 51%	0.005
Bloating	28 (70%)	16 (40%)	30%	8 - 42%	0.009

Results are expressed as percentages, Difference of percentage and 95% Confidence Interval for difference of percentage, †p-value has been calculated through McNemar Test.

Table 4. Gastrointestinal symptoms in female patients on treatment with Spasfon.

	Base line (n=28)	At 8th week end of treatment (n=28)	Difference	95% C.I. for Difference	P-value†
Abdominal Pain	27 (96%)	8 (29%)	67%	43 - 68%	< 0.0001
Frequency of stool (≥3 per day)	16 (57%)	1 (4%)	53%	30 - 54%	0.003
Straining	12 (43%)	9 (32%)	11%	0 - 27%	0.505
Urgency	22 (79%)	6 (21%)	57%	33 - 57%	0.002
Sense of incomplete defecation	24 (86%)	13 (46%)	39%	0 - 31%	0.003
Mucus	10 (36%)	1 (4%)	32%	7 - 38%	0.016
Bloating	20 (71%)	13 (46%)	25%	0 - 37%	0.070

Results are expressed as percentages, Difference of percentage and 95% Confidence Interval for difference of percentage, †p-value has been calculated through McNemar Test.

bowel disease including Crohn's disease and ulcerative colitis. Baseline investigations included complete blood count (CBC), erythrocyte sedimentation rate, stool detail report, serum aminotransferase level (ALT), total bilirubin, creatinine and flexible sigmoidoscopy. Follow-up investigations done on follow-up visit i.e. on completion of eight weeks included CBC, creatinine and ALT. No formal sample size calculation was done for the study and numbers depended on the availability of patents. Informed consent was taken from each patient before entering in the trial. Patients recorded their symptoms in a dairy during pre-treatment and during treatment for eight weeks period. They were called as out-patients and symptoms were reviewed. The various efficacy variables which were assessed are shown in Table 2.

Statistical Analysis was carried out using SPSS software. McNamar's test was used to compare abdominal pain, frequency of bowel movement more than 3 per day, straining, urgency, sense of incomplete evacuation, passage of mucus per rectum and bloating pre and post treatment. Results were expressed as percentages, difference of percentage and 95% Confidence Interval for difference of percentage, †p-value was calculated through McNamar's Test.

Results

One hundred patients were enrolled in the study. Of them 61% (61/100) were males and 39% (39/100) females. Their mean age was 41±14 years. Sixty-eight patients completed the study and 32 dropped out. Of these 26 patients were stationed out of the city. Three patients had drug related side effects with two patients experiencing new onset headache and one allergic reaction. Three patients did not complete the follow-up period and were excluded from the study.

There was relief in most of the features of IBS on treatment with Phloroglucinol (Table 2). There was significant improvement in abdominal pain ($p<0.001$), frequency of stools per day ($p<0.001$), urgency ($p<0.001$), passage of mucus per rectum ($p<0.001$), sense of incomplete defecation ($p=0.001$) and bloating ($p=0.001$) (Table 2). However, no response was seen in the feature of straining ($p=0.676$) (Tables 2 and 4).

There was significant improvement among male patients in abdominal pain ($p<0.0001$) followed by passage of mucus, frequency of stools per day, urgency and bloating (Table 3). Among females there was also significant improvement in abdominal pain ($p<0.0001$) followed by urgency, frequency of stool per day and sense of incomplete defecation (Table 4).

There was an overall positive response to Phloroglucinol in sense of incomplete defecation: however according to gender it was only relieved significantly in female patients ($p=0.003$) (Table 4).

Discussion

The establishment of a strong patient-physician relationship and reassurance form the key initial steps in the management of IBS patient. The choice among treatment alternatives are based on the predominant bowel habit and on the accompanying symptom complex.

The commonest drugs prescribed for abdominal pain are the so called anti-spasmodics which relax smooth muscle. Some such as dicyclomine and hyoscine are anticholinergic whereas others e.g., mebeverine, alverine citrate have a more direct inhibitory effect on intestinal smooth muscle. Meta-analysis of 26 double blind trials found a significant additional benefit for drug over placebo (average improvement 64% vs 45% on placebo) but individual drug meta-analysis failed to show a significant reduction in pain.

This study has evaluated the effects of phloroglucinol on the symptoms of IBS. The benefit of Phloroglucinol in the management of acute episodes of IBS pain is apparent and few side effects make it a good choice for patients with chronic disorder. It is free from the anticholinergic side effects seen in this class of agents such as constipation or dry mouth which limits their use. There was symptomatic relief in all features of IBS after eight weeks of treatment with Phloroglucinol and this was consistent irrespective of gender except sense of incomplete defecation which was significantly relieved only in the females (Tables 2-4). In an earlier study, mebeverine showed general clinical improvement in 70% of all patients after 3 weeks of treatment.[16] In a double blind placebo controlled crossover study which looked at the bran efficiency in IBS after three months of therapy described a significant symptomatic improvement compared with pretreatment in both the bran treated $p<0.01$ and placebo treated group $p<0.01$.[17] Similarly this study shows that Phloroglucinol is as effective as mebeverine and bran in relieving IBS symptoms. This data also suggests that Phloroglucinol had a marked beneficial effect on abdominal pain associated with IBS. Another local study found Phloroglucinol efficacious in relieving IBS symptoms when compared to mebeverine though the sample size was smaller.[18] However, these results need to be confirmed with a multicentre placebo controlled double blind study comparing outcome.

References

1. Thompson WG., Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disease and functional abdominal pain. Gastroenterol Int 1992;5:75-91.
2. Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, Eds. Rome II. The functional gastrointestinal disorders. Diagnosis, pathophysiology and treatment: a multinational consensus, 2nd ed. McLean; Degnon Associates, 2000.
3. Hungin APS, Whorwell PJ, Tack J, Mearin F. The prevalence patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Alimentary Pharmacol Ther 2003;17:643-50.
4. Mathur A, Tandon BN, Prakash OM. Irritable colon syndrome. J Indian Med Assoc 1966;46:651-55.
5. Jafri W, Yakoob J, Jafri N, Maloni M, Shah HA, Hamid S, Abid S, Hussainy AS. Diagnosis of Irritable Bowel Syndrome in patients evaluated for organic bowel pathology. J Coll Physicians Surg Pak 2004;14:438-39.
6. Kwan AC, Hu WH, Chan YK, Yeung YW, Lai TS, Yuen H. Prevalence of irritable bowel syndrome in Hong Kong. J Gastroenterol Hepatol 2002;17:1180-86.
7. Drossman DA, Zhiming LI, Andruzzi E, Temple RD, Talley NJ, Thompson WG, et al. US householder survey of functional gastrointestinal disorders. Prevalence, socio-demography and health impact. Dig Dis Sci 1993;38: 1569-80.
8. Camilleri M, Choi MG. The irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:3-15.
9. Jafri W, Yakoob J, Jafri N, Maloni M, Hamid S, Shah AH, et al. Irritable Bowel Syndrome in Health Care Professionals in Pakistan. J Pak Med Assoc 2003;53:405-7.
10. Jafri W, Yakoob J, Jafri N. Prevalence of Irritable bowel syndrome in college students. JCPS 2005;15:(in press).
11. Yakoob J, Jafri W, Jafri N, Khan R, Islam M, Beg MA, et al. Irritable bowel syndrome: in search of an etiology: Role of Blastocystis hominis. Am J Trop Med & Hyg 2004;70:383-85.
12. Camilleri M, Prather CM. The irritable bowel syndrome: mechanisms and a practical approach to management. Ann Int Med 1992;116:1001-8.
13. Mory B, Poynard T, Naveau S, Chaput JC. Epidemiology and methodology of randomized therapeutic trials in patients with intestinal functional disorders. Gastroenterol Clin Biol 1990;14:58-64.
14. Cargill G, Salin B, Lubin S, Kohler F, Corte T, Rautoreau J, et al. Effect of phloroglucinol on rectosigmoid motility stimulated by a test meal. Study in patients with irritable bowel syndrome. Presse Med 1992;21:19-23.
15. Louvel D, Delavaux M, Stautmont G, Camman F, Fioranonti J, Buenol, et al. Intracolonic injection of glycerol: A model for abdominal pain in irritable bowel syndrome? Gastroenterology 1996;110:351-61.
16. Van Outryve M, Mayeur S, Meeus MA, Rosillon D, Hendrickx B, Ceoppens M, et al. A double-blind crossover comparison study of the safety and efficacy of mebeverine with mebeverine sustained release in the treatment of irritable bowel syndrome. J Clin Pharm Ther 1995;20:277-82.
17. Lucey M.R, Clark ML, Lowndes J, Dawson AM. Is bran efficacious in irritable bowel syndrome? A double blind placebo controlled crossover study Gut. 1987;28:221-5.
18. Haroon M, Haroon R, Akram J. Irritable bowel syndrome: A clinical comparison of mebeverine and phloroglucinol. Pak J Gastroenterol 1999;13(1-2).