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Jacobs Journal of Gastroenterology and Hepatology

Research Article

Belladonna Alkaloid/Phenobarbital (Donnatal™) Effective for Treating IBS Symptoms

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Received: 10-18-2014

Accepted: 12-05-2014

Published: 12-19-2014

Background: IBS, characterized by abdominal discomfort, bloating, and abnormal defecation without organic cause, has 10-15% prevalence in the U.S. with females consistently reporting more constipation and abdominal pain. The pathophysiology remains unclear. Treatment tailored towards the most troublesome symptom is likely to be most beneficial. Belladonna alkaloid/phenobarbital (Donnatal™), available since the 1980's, may provide an effective treatment component.

Aims: To evaluate belladonna alkaloids/phenobarbital for alleviating IBS symptoms in patients presenting with both IBS-C and IBS-D.

Methods: Patients were randomized and treated for 4 weeks, double blind, with belladonna alkaloids/phenobarbital, its components alone, or placebo. Endpoints included day and night pain, BM frequency, and clinician global evaluation.

Results: 204 subjects mean age 41.3 (14.7) years with IBS duration of 54.9 (54.8) weeks. 36% were classified as having loose stools, 46% as having constipation, 6% mixed stool pattern, and 12% normal stool pattern. Demographics and baseline values were comparable. Overall test indicated a significant treatment effect (P = 0.019); belladonna alkaloids/phenobarbital patients improved in night pain (P = 0.018), clinician global rating (P = 0.006), and diary night pain free weeks (P = 0.009).

Conclusion: Belladonna alkaloids/phenobarbital treatment significantly reduced night pain in patients with IBS and was judged by clinicians to result in higher global improvement. Our findings suggest that belladonna alkaloids/phenobarbital is an effective addition to the treatment regimen currently offered to patients with IBS.

Keywords: Irritable Bowel Syndrome; Controlled Clinical Trial; Abdominal Pain; Gender Differences; Belladonna Alkaloid; Phenobarbital

Introduction

Irritable bowel syndrome (IBS), characterized by abdominal discomfort, bloating, and abnormal defecation in the absence of any detectable organic cause, has a 10-15% prevalence in the U.S., accounting for up to $1.6 billion in direct costs and $19.2 billion in indirect costs [1,2]. Having no apparent physiologic mechanism or biomarkers, IBS is a functional gastrointestinal disorder involving complex interactions among hyperalgesia, environmental and genetic factors, gut motility, inflammation, and psychological factors [3]. As yet, none of the available therapies address the entire syndrome,

with most traditional therapies focused on alleviating individual symptoms.

Bulking agents appear to improve global IBS symptoms and reduce severity [4,5], but not quality of life [4]. Loperamide improves stool characteristics but not symptoms or abdominal pain [5]. Antispasmodics were shown by meta-analysis to reduce symptoms by 30% compared with placebo[6].

Lubiprostone was approved for women presenting primarily with constipation with reports of nausea ranging from 5 to 10 times the incidence as placebo [7]. Linaclotide has incident diarrhea in up to 4.5% of users [8]. Two 5-HT receptor agonists – alosetron for diarrhea (IBS-D) and tegaserod (IBS-C) - were removed from the market due to concerns about risk for gastrointestinal and cardiovascular safety [1,9]. Tricyclic anti-depressants have shown some benefit but can cause sedation, dizziness, and orthostasis. [1,10]. Selective serotonin reuptake inhibitors (SSRIs) are effective in some patients but can result in dry mouth, sleep disturbances, or diarrhea [11]. Rifaximin has been successful but with concerns regarding antibacterial resistance [12].

Although available for several years, reviews of the literature rarely include belladonna alkaloid/phenobarbital combination (BA/PH; Donnatal™) [2,6], due in part to the limited sample sizes and variable quality of the studies [13,14]. However, unlike single-mechanism agents, BA/PH is a combination of an anti-spasmodic (belladonna alkaloids) and barbiturate acting on γ-aminobutyric acid (GABA) receptors in the gastrointestinal tract (phenobarbital).

Until more comprehensive and effective alternatives are available, traditional therapies continue to serve an important role managing IBS symptoms. We report the results from a clinical trial designed to compare BA/PH with each component agent and placebo for treating IBS symptoms.

Methods

This masked randomized controlled trial was completed at six centers in the US. The study was approved by Institutional Review Board, and conducted in accordance with Good Clinical Practice guidelines. All patients gave written informed consent.

Eligible patients were randomly assigned to receive: belladonna alkaloids/phenobarbital (BA/PH) 0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, 0.0065 mg hyoscine hydrobromide and 16.2 mg phenobarbital; belladonna alkaloids alone (BA) 0.1037 mg hyoscyamine sulfate, 0.0194 mg atropine sulfate, and 0.0065 mg hyoscine hydrobromide; phenobarbital alone (PH) 16.2 mg phenobarbital; or placebo (PB). Four trial visits occurred at days 1, 8, 15, 22, and 29.

Male and non-pregnant female patients were eligible if in the12 months before the screening visit, they had at least 8 weeks of abdominal pain or discomfort that had ≥ 2 of: (i) relieved with defecation, (ii) onset associated with a change in frequency of stool, and (iii) onset associated with a change in form of stool; and diarrhea, constipation or intermittent constipation/diarrhea at least four times per week for at least one month prior to entering the study (This study was conducted prior to the publication of Rome criteria for IBS typology diagnosis). Patients were excluded with evidence of structural disease, inflammatory bowel disease, simple painless diarrhea, symptoms suggestive of upper GI disease, or concomitant non-GI disease or therapy contraindicating treatment with anticholinergics or barbiturates.

Clinic-based assessments included interrogated IBS symptom ratings including nighttime and daytime pain severity, pain, and bowel movement frequency. Clinician global evaluation was collected at each follow-up visit and referenced "pre-study status": worse, no change, minimal improvement, moderate improvement, and marked improvement (categories had operational definitions). A six-day diary included nighttime and daytime with descriptors for each rating.

Statistical Analysis

The analyses were performed with an intent-to-treat (ITT) population. Demographic and baseline values were tested. Within-group change was evaluated with one-sample t-test. An overall significance test was performed on the ranks of the primary endpoint change scores [14]. Nighttime and daytime pain and clinician global evaluation were tested using analysis of covariance (ANCOVA) models with treatment and gender as main effects and baseline values as covariates. Clinician global evaluations were analyzed as change from pre-study status. Results were controlled for multiple comparisons by Student-Newman-Keuls techniques.

Nominal pain type was described as: sharp, dull, aching, burning, cramping, and other. Distributions between baseline and LOCF categories were examined by Cramer's v analysis for nominal data [15].

Diary data were aggregated as mean values weekly for day pain, night pain, and pain duration. Pain-free weeks were analyzed by Cochran-Mantel-Haenszel chi-square for repeated tests of independence, comparing BA/PH with each of the other four treatment groups.

Bowel movement frequency was examined as absolute distance from "normal" (1 X day). Change in distance from normal was examined by ANCOVA models. Because Rome criteria were not available, subjects were classified as loose stools (BM frequency from "More than 6 times daily" to "2 times per

day"), constipated ("Once every 2-3 days" to "Less than once in 3 days"), normal ("Once per day") and mixed (self-rated). Change in stool type was evaluated by McNemar's Chi square for each treatment group within gender.

Results

The ITT population comprised 204 subjects: BA/PH (50), PH (53) BA (49), PB (52). Baseline characteristics by treatment group are shown in Table 1. The mean (SD, range) age was 41.3 (14.7, 18-77) years, and 84% were white. The mean (SD) self-reported duration of IBS symptoms was 54.9 (58.1) weeks. The treatment groups did not differ significantly by age, duration of IBS symptoms, or race. Treatment groups did not differ by baseline day or night pain (P-values > 0.418), nor stool type classification at baseline (P = 0.802).

Table 1. Sample Demographics, Baseline Endpoint Values, and IBS by Gender.

Treatment Group[1]	Age (Yrs)	IBS Duration (Wks)	Race	Day Pain[2]	Night Pain[2]
Male/Female	[n] Mean (SD)	[n] Mean (SD)	[N] % White	[n] Mean (SD)	[n] Mean (SD)
BA/PH	[21] 37.2 (12.1) [29] 48.3 (17.9)	[15] 52.5 (62.7) [23] 49.2 (39.4)	[21] 81.0 [29] 82.8	[20] 3.05 (0.61) [29] 3.59 (0.63)	[20] 2.00 (1.08) [29] 1.93 (0.92)
BA	[17] 36.7 (12.9) [36] 40.7 (13.6)	[13] 36.8 (37.4) [25] 45.4 (67.3)	[17] 82.4 [36] 91.7	[17] 3.00 (0.61) [34] 3.50 (0.79)	[17] 2.00 (1.00) [34] 2.18 (0.90)
PH	[20] 43.5 (11.7) [29] 41.5 (15.2)	[22] 56.0 (62.4) [38] 62.2 (61.1)	[20] 65.0 [28] 86.2	[19] 3.05 (0.41) [29] 3.38 (0.82)	[19] 2.26 (1.05) [29] 2.14 (1.03)
PB	[34] 42.4 (15.9) [18] 35.2 (11.3)	[15] 40.4 (43.4) [22] 56.0 (62.4)	[18] 72.2 [34] 88.2	[17] 3.12 (0.78) [33] 3.27 (0.63)	[17] 2.18 (1.19) [33] 2.06 (1.03)
Total	[204] 41.3 (17.7)	[173] 54.9 (58.1)	[204] 83.7	[198] 3.29 (0.702)	[198] 2.09 (0.998)

Treatment Group[1]	IBS Classification[3]			
Male/Female	Loose Stools n (%)	Constipated n (%)	Mixed n (%)	Normal n (%)
BA/PH	[6] 30.0 [16] 55.2	[10] 50.0 [11] 37.9	[2] 10.0 [1] 3.4	[2] 10.0 [1] 3.4
BA	[3] 18.8 [14] 41.2	[9] 56.3 [16] 47.1	[1] 6.3 [1] 8.8	[3] 18.8 [3] 8.8
PH	[7] 36.8 [41] 34.5	[8] 42.1 [13] 44.8	[0] 0.00 [2] 6.9	[4] 21.1 [4] 13.8
PB	[6] 35.3 [9] 27.3	[9] 52.9 [15] 45.5	[1] 5.9 [3] 9.4	[1] 5.9 [6] 18.2
Total	71 (36.0)	91 (46.2)	11 (5.6)	24 (12.2)

1 BA/PH – Belladonna Alkaloid/Phenobarbital; PH – Phenobarbital; BA – Belladonna Alkaloid; PB – Placebo
2 Scale: 0 Absent, 1 Mild, 2 Moderate, 3 Severe, 4 Very Severe
3 Loose Stools – "More than 6 times per day" to "2 times per day"; Constipated "Once every 2-3 days" to "Less than once in 3 days; Mixed – self-reported; Normal – "Once per day" (case report form ratings)

Changes from baseline (visit 1 for clinical global evaluation) were significant for day and night pain, and clinician global evaluation for the BA/PH and BA groups (P-values ≤ 0.001); for day and night pain for the PH group (P-values ≤ 0.001); and for day pain for the PB group (P-values ≤ 0.001).

Overall significance tests revealed significant effects for treatment (P = 0.035) and gender (P = 0.023). Specific treatment effects were examined within genders. After adjustment for multiple comparisons, significant treatment effects for females were found for night pain (P = 0.030) and clinician global evaluation (P = 0.001). A posteriori comparisons indicated that the BA/PH group reported significant improvement compared to the BA, PH, and PB groups, while the BA group was more improved than PB. For clinical global evaluation, both the BA/PH and BA improved significantly more than the PH and PB groups (Table 2).

Table 2. Endpoint Change from Baseline by Treatment Group.

Females

Dependent Variable	Treatment[a]	LS-Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Day Pain - Change	BA/PH	1.420	0.207	1.009	1.831
	BA	1.887	0.205	1.480	2.294
	PH	1.324	0.209	0.908	1.739
	PB	1.524	0.197	1.132	1.915
Night Pain - Change	BA/PH[b]	0.897	0.141	0.616	1.179
	BA	0.786	0.139	0.510	1.063
	PH	0.667	0.143	0.383	0.951
	PB	0.466	0.133	0.200	0.731
Global - Change	BA/PH[c]	0.894	0.215	0.467	1.312
	BA	0.841	0.205	0.434	1.248
	PH	0.168	0.222	-0.274	0.609
	PB	0.122	0.207	-0.290	0.534

Males

Dependent Variable	Treatment[a]	LS-Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Day Pain - Change	BA/PH	1.560	0.141	1.277	1.843
	BA	1.610	0.146	1.316	1.904
	PH	1.649	0.138	1.371	1.927
	PB	1.624	0.151	1.320	1.929
Night Pain - Change	BA/PH	0.672	0.179	0.312	1.032
	BA	1.150	0.187	0.774	1.526
	PH	0.765	0.177	0.408	1.121
	PB	0.764	0.193	0.376	1.151
Global - Change	BA/PH	0.369	0.230	-0.094	0.831
	BA	0.672	0.261	0.148	1.196
	PH	0.668	0.233	0.199	1.137
	PB	0.568	0.246	0.073	1.063

a. BA/PH – Belladonna alkaloid/phenobarbital; BA – Belladonna alkaloid; PH – Phenobarbital; PB - placebo

A significant association between baseline and LOCF pain type was found only for the PH group (Cramer's v = 0.596, P < 0.001); 52.5% of the pain type categories remained the same. The most prevalent type of pain was cramping (57.1%). None of the analyses for the other groups was significant (P ≥

0.149) indicating change in pain type from baseline to LOCF categories. The most prevalent shifts were to dull pain (BA/PH 39.5%, BA 52.3%, PB 40.4%).

Analysis of patient diaries revealed significant gender differences. For females, BA/PH subjects were four times more likely to have day pain-free weeks than the PH group (OR = 4.038, P = 0.011), and twice as likely to have night pain-free weeks as BA (OR = 2.301, P = 0.007; Table 3). However, male BA/PH subjects were one-tenth as likely to have day pain-free weeks as PH (OR = 0.107, P = 0.002; Table 3).

Table 3. Patient Diaries – Pain Free Weeks.

Females
Pain Free Weeks - Days

Treatment Comparison	Odds Ratio	Cochran-Mantel-Haenszel Chi Square	P-Value
BA/PH vs.			
BA	1.918	1.895	0.169
PH	4.038	6.537	0.011*
PB	1.499	0.586	0.444

Pain Free Weeks - Nights

Treatment Comparison	Odds Ratio	Cochran-Mantel-Haenszel Statistic	P-Value
BA/PH vs.			
BA	2.301	7.339	0.007*
PH	1.665	2.535	0.111
PB	1.224	0.233	0.629

* Significant after Sidak correction for multiple comparisons

Males
Pain Free Weeks - Days

Treatment Comparison	Odds Ratio	Cochran-Mantel-Haenszel Chi Square	P-Value
BA/PH vs.			
BA	0.158	4.591	0.032
PH	0.107	9.345	0.002*
PB	0.273	1.467	0.226

Pain Free Weeks - Nights

Treatment Comparison	Odds Ratio	Cochran-Mantel-Haenszel Statistic	P-Value
BA/PH vs.			
BA	0.464	3.174	0.075
PH	0.739	0.373	0.541
PB	0.619	1.094	0.296

* Significant after Sidak correction for multiple comparisons

All treatment groups significantly reduced the absolute distance from normal BM frequency (P-values < 0.001); however the treatment groups did not differ. The proportion of subjects classified as normal at baseline and final visits was examined by McNemar's test by treatment group within gender. Following Sidak adjustment, a significant proportion of BA/PH females shifted to normal (P = 0.002).

Discussion

Although available for several decades, BA/PH is rarely mentioned in IBS therapeutic updates due in part to the quality of previous studies. Yet many of those same reviews recommend that treatment plans be targeted towards patient-specific symptoms.

Our results revealed that BA/PH was effective for treating abdominal pain, especially at night and among women. Patient daily diaries indicated that BA/PH was effective for daytime pain in women as well. BA/PH is not associated with many of the side effects found with other medications, including the sedation often accompanying TCA and SSRI use, antibacterial resistance linked to chronic antibiotic use, and some cardiovascular and gastrointestinal side risks associated with lubiprostone, alosetron, tegaserod, and lubiclotide. Probiotics, loperamide, and fiber target abnormal stool habits but have variable impact on pain.

Although females are overrepresented in IBS diagnosis, other factors, e.g. symptom perception, impact on activities of daily living, and access to healthcare, may also play a role [16,17]. Compounding these are functional disorder symptoms including gastrointestinal motility, pain perception or central nervous system responses, which vary by gender and may be regulated, in part, by hormones [18].

The pathophysiology of IBS suggests possible reasons for gender differences. IBS is a multi-symptom disorder of brain-gut function in which emotional and cognitive areas of the brain modulate symptoms [19,20]. A bi-directional interaction along the brain-gut axis might explain why social and psychological stressors and associated alterations in mood differentially affect the function of the gut and IBS symptoms [21]. The sympathetic and parasympathetic pathways seem to be altered by IBS and increased sympathetic and decreased parasympathetic activation has been shown in men compared with women [22].

While not studied extensively, the evidence indicating important gender differences in IBS has important clinical implications. No single treatment has superior efficacy and multiple treatments tailored to patients' symptoms appear to be a more promising strategy. In this study, reduced pain with BA/PH was robust across methods, suggesting that BA/PH may serve as an effective addition to the treatment regimen for patients with IBS.

This study had a certain limitations. The data were collected before Rome criteria were adopted. However, the symptom eligibility criteria were identical to those used currently for Rome III. Pain or discomfort needed to be relieved in two or more of: (i) relieved with defecation, (ii) onset associated with a change in stool frequency, and (iii) onset associated with change in form of stool. Symptom duration prior to entry was characterized differently in the protocol. Rome III requires pain or discomfort at least 3 days/month in the previous three months.

This study required pain or discomfort "for at least 8 weeks in the previous 12 months."

While we found significant differences between males and females, the study was not stratified by gender during randomization. Although the treatment groups did not differ within gender, stratification would have resulted in a more robust design. While the mean sample sizes for each treatment group within gender were modest (32 for females and 19 for males), the pattern of consistent significant treatment effects supports the overall conclusions regarding pain.

Additionally, there was a large placebo effect, although this is not unique to the current study. Patel [23] reported an average of 40% placebo response in IBS clinical trials. However it may have masked other effects (e.g., day pain relief, BM frequency) that a larger sample size would have illuminated. Some of these important secondary effects may have been revealed with higher quality IBS-specific symptom questionnaires [24] and quality of life assessments [25] which are likely to yield richer patient reported outcomes information.

In conclusion belladonna alkaloids/phenobarbital treatment significantly reduced IBS-related night pain and resulted in overall clinical improvement. These findings suggest that belladonna alkaloids/phenobarbital should be considered as an effective addition to the treatment options currently available for IBS.

Acknowledgement

The authors wish to thank Ms. Lynda Rittaco, Phase V Technologies, Inc., Wellesley Hills, MA, for her data management, data entry and quality control expertise in this project. Support for data management and analysis was provided by a grant from PBM Pharmaceuticals.

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