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Original Article

The Evaluation of Otilonium Bromide Treatment in Asian Patients With Irritable Bowel Syndrome

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Background/Aims
Antispasmodics including otilonium bromide (OB) are recommended to treat irritable bowel syndrome (IBS). However, reports about OB experience in Asia is sparse. The purpose of present study was to provide the efficacy of OB in treating Asian IBS patients.

Methods
Overall, 117 IBS patients meeting Rome II criteria were enrolled in an 8-week, double-blind, active-controlled and single center trial. Randomized participants received either OB 40 mg or mebeverine 100 mg 3 doses daily. The primary endpoints were to evaluate the net changes of abdominal pain/discomfort frequency score (APDFS) and safety profile, while the secondary endpoints were to assess the changes in abdominal pain/discomfort intensity, flatulence, abdominal bloating, satisfied stool frequency etc.

Results
Finally, 49 OB and 52 mebeverine subjects were eligible for efficacy analysis. Compared to baselines in per protocol populations, the reduced APDFSs in OB and mebeverine were 0.55 ± 1.20 (P = 0.011) and 0.37 ± 1.11 (P = 0.042), respectively, to show similarly reduced scores. The most reported side effects included dry mouth, nausea and dizziness. Besides, the improved APDFSs at 4th week visit, final alleviations in abdominal pain intensity, flatulence, abdominal bloating and satisfied stool frequency with global assessments filled by both patients and investigators were significantly achieved by both treatments, and OB was not inferior to mebeverine in treating these parameters.

Conclusions
In Orientals, OB is as effective as mebeverine for alleviating IBS symptoms in terms of abdominal pain, flatulence, abdominal bloating etc. However, obvious side effects are also observed. A large-scaled trial and post-marketing surveillance are recommended to confirm its efficacy and safety.
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Key Words
Abdominal pain; Irritable bowel syndrome; Mebeverine; Otilonium bromide

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Introduction

Irritable bowel syndrome (IBS) refers to a functional gastrointestinal (GI) disorder characterized by the abdominal pain/discomfort that is associated with disturbed bowel movement (BM) in terms of stool frequency and consistency.[1,2] Currently, the true IBS pathophysiology remains enigmatic since many mechanisms have been addressed but not well agreed. For example, the most mentioned mechanisms include GI dysmotility, autonomic nervous dysfunction, visceral hypersensitivity, gut immune dysfunction, neuropeptide receptor dysfunction, brain-gut dysfunctional linkage, genetic polymorphism, psychological disorders etc.[3-7] Clinically, IBS *per se* has a profound impact on the living and quality of life leading to the excessive use of medical resources.[2,8-10] The up-to-date IBS treatment strategy recommends a positive diagnosis, consideration of the patients' agenda and emotional state, continuous care and evaluations on graded therapeutic responses.[1,3,6,10,11] Unfortunately, many available treatments are not globally agreed and accepted between countries, medical payers and patients, while IBS subjects are often not satisfactory to those treatments.[5,11,12] Newly developed drugs targeted on receptors are emerging, however, current IBS guidelines still recommend antispasmodics in diminishing pain/discomfort severity although these agents have been launched for decades.[2,3,5,6,10,13] Meta-analysis indicates again that smooth muscle relaxants are effective in reducing abdominal pain and global symptom compared to the placebo.[14]

Among the antispasmodics, otilonium bromide (OB) is claimed to reduce the IBS pain severity effectively.[3,10,12] Pharmacologically, OB is one of the quaternary ammonium derivatives with GI smooth muscle spasmolytic activity via inhibition of calcium ion influx through L-type voltage operated calcium channels.[15,16] European studies already confirmed OB in relieving IBS pain/discomfort.[17,18] Interestingly, reports on its experiences in Asia are not existed. Therefore, we conducted a single center, double-blind, randomized, active drug-controlled trial in looking its efficacy. The primary endpoints were to evaluate the improvement of abdominal pain/discomfort frequency score (APDFS) and drug safety under an 8-week OB treatment. The secondary endpoints were to assess the OB efficacies by (1) the net change of the 4th week evaluation compared to the baseline APDFS, (2) the net change of the 8th week evaluation compared to the baseline abdominal pain/discomfort intensity severity, (3) the changes of other IBS parameters including flatulence, abdominal bloating and satisfied stool frequency and (4) the global assessments after treatment filled by both the investigators and patients.

Materials and Methods

Enrolled Subjects

This study was conducted between November 2003 and January 2006. Briefly, eligible subjects aging 20-80 year who presented with bowel symptoms fulfilling Rome II criteria in the Outpatient Department of Taipei Veterans General Hospital were consecutively invited and considered to participate in this trial.[19] Alarm symptoms and signs such as fever, bloody stool, persistent diarrhea, marked body weight loss and anemia were excluded. Colon imaging study using either barium enema or colonoscopy within the previous year should be normal in the subjects (age $\geq$ 40 years). Other criteria of exclusion included pregnant or breastfeeding women, history of malignancy within 5 years, gut surgery except appendectomy, malabsorption diseases, hyper- or hypothyroidism, abnormal renal or liver function tests, inflammatory bowel diseases, connective tissue diseases, severely progressive diseases, diabetes, obvious psychiatric disorders, substance abuse, unable to discontinue drugs known to influence gut motility, using iron supplements or colchicine, concurrently participating in another study etc. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and Department of Health, ROC, while informed consent was obtained from all participants prior to the recruitment.

Study Design

This study was designed as a double-blind, randomized, parallel and comparative trial. We expected to assign about 40 assessable subjects to each of 2 study arms. Under consideration of probable withdrawal, at least 100 IBS subjects (50 in each arm) were planned to enroll. During the screening visit (14 days prior to the first treatment day), demographic data, vital signs, general physical examinations, concomitant medications, medical history, concurrent diseases, laboratory and pregnancy tests and current IBS symptoms were obtained. After this visit, all the prohibited drugs were held at least 1 week prior to the randomization. On day 1 of visit 2, treatment assignment was based on pre-generated permuted block randomization scheme. The block size of four was used to enroll subjects with a 1:1 ratio of the OB arm to controlled mebeverine arm. Clinical evaluation was performed again to confirm the eligibility and to record the IBS symptomatic

baselines. After randomization, the eligible subjects were provided with a patient diary record and were treated using either OB or mebeverine for a total of 8 weeks in a double-blind method. They were instructed to come back for the 3rd visit at the end of 4th week (within ± 5 days treatment window) after randomization. Similar clinical evaluation was performed to assess their treating efficacy and safety. Patient's diary record was collected and a new card was given again. Unused study medications were collected to document drug accountability. Each subject was prescribed with the similarly coded medications for another 4-week treatment period. Final visit was performed at the end of 8th week after randomization. The efficacy and adverse events were recorded again. The global assessments filled by the investigators and patients were acquired. Consumption of concomitant medications during the entire study period was documented. Laboratory and pregnancy tests were repeated to confirm the study safety.

Study Drugs and Rescue Agents

A double-blind and double-dummy method was used in this study to achieve the double masking. For instance, OB active tablet (40 mg, batch no. ML157011; YL115128/YL115129) and its matching placebo tablet were prepared to be identical in all aspects. While mebeverine HCl active tablet (100 mg, bath no. 310991) and its matched placebo tablet were similarly manufactured to be unidentifiable. Subjects in the OB arm were instructed to consume one tablet of OB plus 1 tablet of mebeverine placebo simultaneously 3 times daily 30 minutes before the meals. Subjects assigned to the mebeverine arm were instructed to consume one mebeverine tablet plus one OB placebo tablet 3 times daily before the meals. All the study products and placebo were supplied under the responsibility of TTY Biopharm Co, Ltd (Taipei, Taiwan). The frequency to supply study drugs to the study site was adapted to the expiry date of products. Rescue agent such as loperamide one tablet daily was allowed to the subject who suffered from intractable diarrhea (> 3/day for 3 days) during the trial. On the other hand, bisacodyl 2 tablets daily was allowed for subject who suffered from annoying constipation (no BM > 3 days).

Symptomatic Assessments and Safety Recording

The primary efficacy variable was to measure the change in APDFS after 8 weeks of treatment. Based on the diary card, the APDFS was categorized into four grades: score 0 = none; score 1 = ≤ 3 episodes per week; score 2 = 4-7 episodes per week; and score 3 = > 7 episodes per week. The APDFS scored at visit 2 served as baseline and was re-evaluated at the ends of 4th and 8th week after treatment, respectively. The abdominal pain/discomfort intensity was subjectively scored into four categories: score 0 = absent; score 1 = mild; score 2 = moderate; and score 3 = severe. Besides, a 10 cm visual analog scale (VAS) to record grades of flatulence, abdominal bloating and satisfied stool frequency by the subjects was instructed by oral and written information before the assessment. The 0 cm end means "no symptom" or "normal," whereas the 10 cm end indicates the "worst bowel symptom" or "most intolerable." Abdominal pain/discomfort intensity and VAS scores at visit 2 served as the baselines and the differences of pre- and post-treatment VAS scores at final visit were used for the secondary endpoints. At the final visit, subjects and investigators completed a global assessment to the overall responses after trial, respectively. The global assessment was a 5-point scale, using the following definition: 0 = worsened, 1 = no change, 2 = slightly improved, 3 = improved and 4 = significantly improved. Throughout the study, the investigators closely monitored and recorded the probable occurrences of any adverse event (AE) after visit 2. All the AEs that occurred in subjects who took at least 1 dose of study medication were recorded in detail. The relationship of AE to study medication was also defined.

Statistical Methods

All subjects who had consumed at least one dose of study medication and had at least one post-treatment evaluation on the primary endpoints were included in the intent-to-treat (ITT) population analysis. Furthermore, the per-protocol (PP) population consisted of all ITT subjects who did not take any violated medications and had completed at least 28 days of treatment.

The primary endpoint was $APDFS_{difference}$ or APDFS at baseline APDFS at 8th week. The primary hypothesis was: H0: $\mu t-\mu s \leq -0.35$ Ha: $\mu t-\mu s > -0.35$. While H0 means null- hypothesis and Ha means alternative-hypothesis; μt means the $APDFS_{difference}$ of the net OB response and μs denotes the $APDFS_{difference}$ of the net mebeverine response. Treatment arm was declared as non-inferior if the difference in lower limit of 97.5% one-sided confidence interval (CI) calculated by either t test or Wilcoxon rank sum test between treatments was greater than -0.35. Results were expressed as mean ± SD or median with inter-quartile range (IQR) when appropriate. Categorical differ-

ence was based on chi-square test or Fisher's exact test when appropriate. The net changes of various parameters used for secondary endpoints were analyzed using either *t* test or Wilcoxon rank sum test to compare between treatments. Intra-assay difference was calculated using Wilcoxon signed rank test. Global assessment by the investigators and subjects was analyzed using Mantel-Haenszel test to compare the differences between treatments. All the statistical tests were 2-tailed and the *P*-value less than 0.05 was considered significant.

Results

Totally, 132 IBS subjects fulfilling Rome II criteria gave informed consent and were screened, and only 117 subjects were eligible to be randomized and treated (Figure). All these randomized subjects had consumed at least 1 dose of study medication. However, 16 subjects had violated ITT criteria and only 101 subjects were enrolled in the ITT population including 49 in OB arm and 52 in mebeverine arm. Twenty subjects in the ITT population were excluded from the PP population based on our definition. Finally, 81 subjects (38 OB:43 mebeverine) were eligible in the PP population. Table 1 depicts the demographic characteristics and baseline IBS symptoms of both arms. There were no differences in terms of age, gender, body mass index, IBS duration, proportions of IBS subtypes, abdominal pain/discomfort severity etc. Overall, the treatment compliances of OB

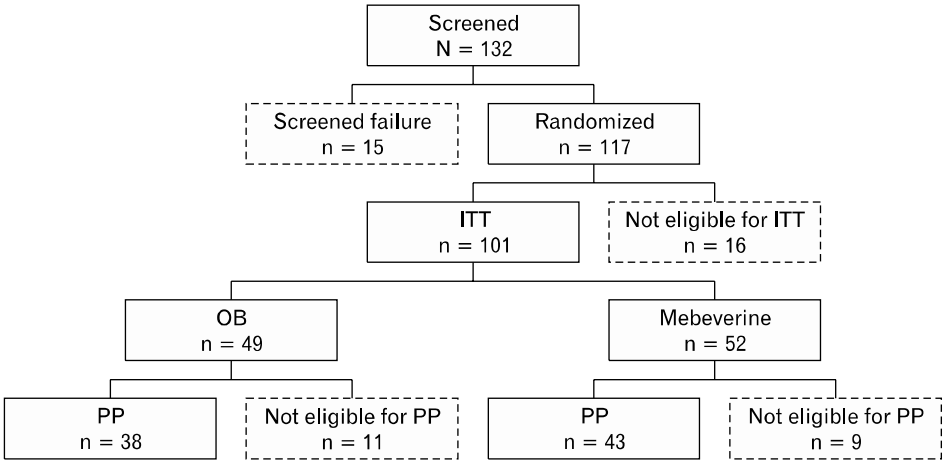

Figure. Trial overview including enrollment, randomization and follow-up among the irritable bowel syndrome patients fulfilling Rome II definition. Dot lined squares mean the numbers of subject excluded from analysis. ITT, intention-totreat; OB, otilonium bromide; PP, per-protocol.

Table 1. The Demographic Characteristics and Baseline Clinical Manifestations of Enrolled Irritable Bowel Syndrome Patients

	Otilonium bromide (n = 59)	Mebeverine (n = 58)	*P*-value
Male gender (n [%])	31 (52.5)	26 (44.8)	0.461
Age (yr)	51.5 ± 16.5	54.4 ± 16.0	0.308
BMI (kg/m^2)	22.1 ± 2.9	22.5 ± 3.5	0.493
IBS duration (yr),	7.1 ± 7.7	8.6 ± 7.5	0.081
Median (95% CI)	4.0 (3-7)	5.4 (4.6-10)	
IBS subtype (n [%])			0.140
Diarrhea	34 (57.6)	42 (72.4)	
Constipation	22 (37.3)	12 (20.7)	
Mixed	3 (5.1)	4 (6.9)	
Abdominal pain/discomfort frequency score[a]	2.02 ± 0.99	2.08 ± 0.95	0.785
Abdominal pain/discomfort intensity score[a]	1.20 ± 0.41	1.17 ± 0.47	0.599
Flatulence VAS score (0-10 cm)	5.26 ± 2.53	4.47 ± 3.06	0.523
Abdominal bloating VAS score (0-10 cm)	5.58 ± 3.01	4.75 ± 3.38	0.255
Satisfied stool frequency VAS score (0-10 cm)	6.17 ± 2.72	6.59 ± 2.88	0.373

[a]Abdominal pain/discomfort frequency score with 4-score severity divided as score 0 = none, score 1 = ≤ 3 episodes per week, score 2 = 4-7 episodes per week and score 3 = > 7 episodes per week.
BMI, body mass index; IBS, irritable bowel syndrome; VAS, visual analog scale using 10 cm scale.
Data are presented as mean ± SD.

and mebeverine arms were 88.9% ± 13.0% and 90.4% ± 11.6%, respectively (NS), while the mean daily doses of using study drugs were 2.60 ± 0.47 and 2.66 ± 0.44 units, respectively (NS). On the other hand, the numbers of patient who consumed rescue agent at least once during the trial were 49 (100%) and 51 (98.1%), respectively (NS). The total numbers of consumed loperamide among both arms were 2.89 ± 0.32 and 3.05 ± 0.53, respectively (NS), whereas the numbers of consumed bisacodyl were 3.13 ± 0.97 and 2.93 ± 0.26, respectively (NS).

Briefly, about 40 % of subjects had APDFS improvement under either OB or mebeverine treatment based on ITT and PP populations (Table 2). Likewise, the mean reduced APDFS scores in the OB arm were 0.39 ± 1.32 ($P = 0.056$) and 0.55 ± 1.20 ($P = 0.011$) based on ITT and PP populations, respectively. However, the net APDFS reduced scores in the mebeverine arm were 0.40 ± 1.16 ($P = 0.023$) and 0.37 ± 1.11 ($P = 0.042$) based on ITT and PP populations, respectively. None of the improved data showed statistically significant differences between 2 treatments. The lower bound of 95% CI of treatment difference was over the hypothesized set margin (-0.35) in both ITT and PP populations. Accordingly, we concluded that OB was at least comparable to mebeverine in reducing APDFS at final visit. Regarding the drug safety, 118 AEs had been reported including 65 in OB and 53 in mebeverine. Among them, dry mouth was the most reported event in both treatments followed by nausea and dizziness particularly in OB treatment arm (Table 3). Most AEs were mild to moderate in nature (89.2% in OB; 88.7% in mebeverine), whereas 3 subjects (5.1%) in OB and 5 subjects (8.6%) in mebeverine were withdrawn owing to the intolerable AEs. Besides, 2 OB subjects (1 renal stone; 1 coronary heart disease) and 2 mebeverine subjects (1 amnesia; 1 herniated inter-vertebral disc) were hospitalized during the trial. All these serious AEs judged by the investigators were unlikely related to the study. On regarding the changes in terms of hematology, biochemistry, vital signs and physical examinations of 2 arms, there were no differences compared to the baselines.

With regard to the 2nd endpoints, Table 4 illustrates the net APDFS changes at 4th week evaluation. The mean APDFS reduced scores for OB and mebeverine were 0.12 ± 1.32 ($P = 0.545$) and 0.31 ± 1.08 ($P = 0.072$), respectively, based on ITT populations without differences between 2 arms. The mean changed scores of PP populations were 0.24 ± 1.36 ($P = 0.276$) and 0.33 ± 1.04 ($P = 0.70$), respectively, without differences between 2 arms. The net changes of the patient numbers at final evaluation on the abdominal pain/discomfort intensity are illustrated in Table 5. Overall, the mean reduced intensity scores in OB arm were 0.41 ± 0.57 ($P < 0.001$) and 0.45 ± 0.60 ($P <$

Table 2. The Numbers of Patients With Net Changes in 8th Week Evaluation Compared to Baseline Abdominal Pain/Discomfort Frequency Score (APDFS) Assessment in Irritable Bowel Syndrome Patients After Treatment

	Otilonium bromide	Mebeverine	*P*-value
	ITT (n = 49)	ITT (n = 52)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	5 (10.2)	3 (5.8)	
-1 score (%)	4 (8.2)	6 (11.5)	
0 (%)	21 (42.9)	20 (38.5)	
+1 score (%)	8 (16.3)	16 (30.8)	
+2 score (%)	8 (16.3)	4 (7.7)	
+3 score (%)	3 (6.1)	3 (5.8)	
Median (IQR)	0.00 (1.00)	0.00 (1.00)	0.890
95% CI	(0.00; 1.00)	(0.00; 1.00)	
	PP (n = 38)	PP (n = 43)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	2 (5.3)	2 (4.7)	
-1 score (%)	3 (7.9)	5 (11.6)	
0 (%)	16 (42.1)	19 (44.2)	
+1 score (%)	8 (21.1)	11 (25.6)	
+2 score (%)	7 (18.4)	4 (9.3)	
+3 score (%)	2 (5.3)	2 (4.7)	
Median (IQR)	0.00 (1.00)	0.00 (1.00)	0.479
95% CI	(0.00; 1.00)	(0.00; 1.00)	

APDFS: abdominal pain/discomfort frequency score with 4-score severity divided as score 0 = none, score 1 = ≤ 3 episodes per week, score 2 = 4-7 episodes per week and score 3 = > 7 episodes per week; baseline: on day of randomization; score of net change: APDFS (baseline-8th week).
ITT, intention-to treat; IQR, inter-quartile range; PP, per-protocol.

Table 3. Commonly Reported Adverse Events Among the Irritable Bowel Syndrome Patients With at Least One Dose of Treatment

Event (%)	Otilonium bromide (n = 59)	Mebeverine (n = 58)	*P*-value
Dry mouth	11 (18.6)	13 (22.4)	0.650
Nausea	8 (13.6)	0 (0.0)	0.006
Dizziness	6 (10.2)	1 (1.7)	0.110
Sore throat	4 (6.8)	4 (6.9)	1.000
Skin itching	2 (3.4)	3 (5.2)	0.680
Myalgia	2 (3.4)	0 (0.0)	0.490
Malaise	2 (3.4)	0 (0.0)	0.490
Headache	1 (1.7)	3 (5.2)	0.360
Abdominal pain	1 (1.7)	2 (3.4)	0.620
Insomnia	1 (1.7)	0 (0.0)	1.000

Table 4. The Numbers of Patients With Net Changes in 4th Week Evaluation Compared to Baseline Abdominal Pain/Discomfort Frequency Score (APDFS) Assessment in Irritable Bowel Syndrome Patients Who Received Treatment

	Otilonium bromide	Mebeverine	*P*-value
	ITT (n = 49)	ITT (n = 52)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	6 (12.2)	4 (7.7)	
-1 score (%)	9 (18.4)	2 (3.8)	
0 (%)	17 (34.7)	28 (53.8)	
+1 score (%)	9 (18.4)	12 (23.1)	
+2 score (%)	6 (12.2)	4 (7.7)	
+3 score (%)	2 (4.1)	2 (3.8)	
Median (IQR)	0.00 (2.00)	0.00 (1.00)	0.365
95% CI	(0.00; 0.00)	(0.00; 0.00)	
	PP (n = 38)	PP (n = 43)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	4 (10.5)	3 (7.0)	
-1 score (%)	7 (18.4)	2 (4.7)	
0 (%)	13 (34.2)	22 (51.2)	
+1 score (%)	6 (15.8)	11 (25.6)	
+2 score (%)	6 (15.8)	4 (9.3)	
+3 score (%)	2 (5.3)	1 (2.3)	
Median (IQR)	0.00 (2.00)	0.00 (1.00)	0.588
95% CI	(0.00; 1.00)	(0.00; 1.00)	

APDFS: abdominal pain/discomfort frequency score with 4-score severity divided as score 0 = none, score 1 = ≤ 3 episodes per week, score 2 = 4-7 episodes per week, and score 3 = > 7 episodes per week; baseline: on day of randomization; score of net change: APDFS (baseline-4th week).
Abbreviations as in Table 2.

Table 5. The Numbers of Patients With Net Changes in 8th Week Evaluation Compared to Baseline Abdominal Pain/Discomfort Intensity Scored in the Irritable Bowel Syndrome Patients After Treatment

	Otilonium bromide	Mebeverine	*P*-value
	ITT (n = 49)	ITT (n = 52)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	0 (0.0)	0 (0.0)	
-1 score (%)	0 (0.0)	0 (0.0)	
0 (%)	31 (63.3)	39 (75.0)	
+1 score (%)	16 (32.7)	9 (17.3)	
+2 score (%)	2 (4.1)	4 (7.7)	
+3 score (%)	0 (0.0)	0 (0.0)	
Median (IQR)	0.00 (1.00)	0.00 (0.50)	0.289
95% CI	(0.00; 1.00)	(0.00; 0.00)	
	PP (n = 38)	PP (n = 43)	
-3 score (%)	0 (0.0)	0 (0.0)	
-2 score (%)	0 (0.0)	0 (0.0)	
-1 score (%)	0 (0.0)	0 (0.0)	
0 (%)	23 (60.5)	33 (76.7)	
+1 score (%)	13 (34.2)	7 (16.3)	
+2 score (%)	2 (5.3)	3 (7.0)	
+3 score (%)	0 (0.0)	0 (0.0)	
Median (IQR)	0.00 (1.00)	0.00 (0.00)	0.162
95% CI	(0.00; 1.00)	(0.00; 0.00)	

Four-score of abdominal pain/discomfort intensity: score 0 = absent, score 1 = mild, score 2 = moderate and score 3 = severe; baseline: on day of randomization; score of net change: Abdominal pain/discomfort intensity score (baseline-8th week).
Abbreviations as in Table 2.

0.001), and the mean reduced intensity scores in mebeverine arm were 0.33 ± 0.62 ($P = 0.001$) and 0.30 ± 0.60 ($P = 0.004$), respectively, based on ITT and PP populations. None of the above data showed statistical difference between 2 arms. Other changes of IBS symptoms in terms of flatulence, abdominal bloating and satisfied stool frequency are depicted in Table 6. Briefly, these evaluated bowel symptoms had marked improvement after both treatments, on either ITT or PP analysis, while the changes in abdominal bloating and satisfied stool frequency were similar in both groups (data were not shown). Table 7 denotes the global symptom assessments filled at final visit. Regarding ITT population, the proportions of at least slight improvement of OB and mebeverine evaluated by the investigators were 87.8% and 76.9%, respectively (NS), whereas those of PP population were 86.8% and 74.4%, respectively (NS). By the patients, the proportions of subjects with at least slight improvement of OB and mebeverine were 89.8% and 78.8% ($P < 0.05$), respectively, in

Table 6. The 10 cm Visual Analog Scale Scored Bowel Symptoms of Irritable Bowel Syndrome Patients After Either Otilonium Bromide or Mebeverine Treatment

Symptom	OB		Mebeverine	
	ITT (n = 49)	PP (n = 38)	ITT (n = 52)	PP (n = 43)
Flatulence				
Baseline (visit 2)	5.6 (3.6)[a]	5.3 (3.9)[b]	3.6 (5.4)[c]	3.0 (5.4)[d]
Final	2.0 (2.7)[a]	1.6 (2.8)[b]	2.0 (4.1)[c]	1.6 (4.4)[d]
Abdominal bloating				
Baseline (visit 2)	5.1 (4.2)[e]	4.4 (3.9)[f]	4.7 (6.6)[g]	4.5 (7.0)[h]
Final	1.7 (3.3)[e]	1.3 (3.2)[f]	1.3 (4.6)[g]	1.3 (4.8)[h]
Satisfied stool frequency				
Baseline (visit 2)	5.0 (5.0)[i]	4.2 (4.2)[j]	4.8 (5.3)[k]	4.6 (5.5)[l]
Final	1.5 (2.9)[i]	1.4 (2.4)[j]	1.7 (3.9)[k]	1.8 (4.0)[l]

OB, otilonium bromide; ITT, intention-to-treat; PP, per-protocol.
Results are median (inter-quartile range). Inter-assay difference: [a-c,e-l]$P < 0.001$, [d]$P = 0.003$.

Table 7. Global Assessment Respectively Filled by the Investigators and Irritable Bowel Syndrome Patients at the Final Visit After Treatment

	Otilonium bromide	Mebeverine	*P*-value[a]
Investigator assessment	ITT (n = 49)	ITT (n = 52)	0.089
Worsen	1 (2.0)	0 (0.0)	
No change	5 (10.2)	12 (23.1)	
Slightly improved	11 (22.4)	14 (26.9)	
Improved	15 (30.6)	14 (26.9)	
Markedly improved	17 (34.7)	12 (23.1)	
Investigator assessment	PP (n = 38)	PP (n = 43)	0.071
Worsen	1 (2.6)	0 (0.0)	
No change	4 (10.5)	11 (25.6)	
Slightly improved	7 (18.4)	10 (23.3)	
Improved	11 (28.9)	12 (27.9)	
Markedly improved	15 (39.5)	10 (27.9)	
Patient assessment	ITT (n = 49)	ITT(n = 52)	0.046
Worsen	0 (0.0)	0 (0.0)	
No change	5 (10.2)	11 (21.2)	
Slightly improved	14 (28.6)	18 (34.6)	
Improved	18 (36.7)	16 (30.8)	
Markedly improved	12 (24.5)	7 (13.5)	
Patient assessment	PP (n = 38)	PP (n = 43)	0.042
Worsen	0 (0.0)	0 (0.0)	
No change	5 (13.2)	9 (20.9)	
Slightly improved	8 (21.1)	16 (37.2)	
Improved	15 (39.5)	12 (27.9)	
Markedly improved	10 (26.3)	6 (14.0)	

ITT, intention-to-treat; PP, per-protocol.
Data are presented as n (%). [a]Based on Mantel-Haenszel test.

the ITT populations and 86.8% and 79.1% ($P < 0.05$), respectively, in the PP populations.

Discussion

Mebeverine has long been marketed in Asia as an antispasmodic to treat IBS for decades. Using it as an active-controlled agent, our study based on the primary endpoint mainly indicated that OB was as effective as mebeverine in improving the APDFS of represented IBS main symptoms during an 8-week period treatment. Our previous study pointed out that mebeverine was effective in reducing BM frequency and stool consistency for the diarrhea-predominant IBS patients but no obvious effect for abdominal pain.[20] Besides, a meta-analysis also indicates that mebeverine has no global effect to treat IBS abdomen pain compared to the placebo although it is tolerable without obvious side effects.[21] It is believed that placebo does exhibit an amazing efficacy to treat IBS patients with range of 20%-50%.[3,22] Accordingly, an agent shown superior to placebo in treating IBS should be obtained from a large-scaled study or meta-analysis, eg, the tegaserod trials.[23] Owing to the comparable efficacy to placebo, it is likely that many mebeverine studies including our previous trial do not confirm its perfect efficacy to treat abdominal pain, one of the IBS main symptoms.

Since abdominal pain/discomfort has been a very subjective complaint to IBS patients, it would be difficult to quantify it using any reliable parameters.[2] In addition, as the abdominal pain scales in many trials are often recorded by the recalled manner, it is unknown whether any pain character recording does reflect the true sensation on the assigned visits after several days or weeks. In order to diminish this drawback, we employed the APDFS based on recorded pain frequency in the distributed diary card and tried to describe the pain character more objectively for the primary endpoint. Based on APDFS, our primary objective did confirm a fair but not perfect efficacy of OB comparable to mebeverin in reducing the IBS abdominal pain frequency. In addition, another parameter of abdominal pain intensity score also confirmed the at least equal OB efficacy to mebeverine. The rationale of using antispasmodics to treat IBS is likely based on the observations of disturbed GI motility among these patients.[2,4,12,24] Actually, bowel dysmotility does result in functional abdominal pain among the IBS patients.[3,25] Unfortunately, the central sensation of visceral pain is not uniquely related to the disturbed GI motility. It means that many biopsychosocial factors like mind, environmental factors, visceral hypersensitivity and brain-gut interaction may modify the final pain perception for the patients with functional GI disorders including IBS.[1,26] Because of the excessive confounding factors in modifying the central pain sensation with heterogeneity in published studies, many antispasmodic trials cannot conclude a perfect efficacy to treat the abdominal pain, while the comparable placebo does achieve a similar efficacy. Sometimes, only the meta-analysis can summarize its possible efficacy.[3,14]

Among researches on the OB efficacy on IBS patients, an early small-scaled study conducted in Italy indicated that OB did reduce the abdominal pain and bloating but no differences were observed from placebo.[27] Consequently, a large-scaled placebo controlled trial among the Italian IBS patients indicated that the reduced episode of abdominal pain was higher in OB treated patients (55.3%) than in placebo group (39.9%), while the fair efficacies were observed for the abdominal distension and general well-being among those on OB treatment.[17] Nevertheless, the au-

thors did not particularly address the probable side effects in that trial. A review based on 4 OB trials then concluded that OB may relieve IBS symptoms with a relative risk of 0.55 (95% CI, 0.310-0.097) over placebo.[28] Currently, OB has been recommended as an effective and safe agent to treat IBS abdominal pain and distension, particularly in reducing diarrhea, whereas the most addressed side effect is urticaria.[29] In addition to the reduction in IBS abdominal pain, our OB study did confirm the similar efficacies including improved abdomen bloating, flatulence, satisfied BM frequency and global assessments.

Apart from blocking the calcium ion influx through L-type voltage operated calcium channels in GI smooth muscle cells, OB pharmacologically inhibited central/peripheral tachykinin-2 receptor which not only showed antispasmodic activity but also reduced the afferent transmission of sensory signals from the periphery to central nervous system.[15,30] It is of interest whether this tachykinin receptor blocking ability in the afferent transmission reduce the IBS pain severity or not. In fact, a clinical trial did confirm that OB enhanced the perceptual threshold of IBS subjects during the anorectal balloon distension.[31] Since visceral hypersensitivity has been one of the main components of the IBS pathogeneses,[2,3] OB is therefore possible to treat the IBS main symptom apart from its antispasmodic effect. In addition, OB also shows a high affinity in binding to various muscarinic receptor subtypes in terms of M1, M2, M3, M4 and M5, respectively.[32,33] Owing to its potent muscarinic blockade, OB not only exhibit an antispasmodic but also antisecretory ability through M3 sub-receptor which is abundantly found in human colonic crypt cells to mediate secretion coupled with calcium channels.[33] It is why OB can improve the stool consistency.[18,29] Furthermore, both M1 and M3 sub-receptors have been the main targets of nervous impulse to mediate salivary gland secretion.[34] Because OB also targets on these muscarinic sub-receptors, the most observed AE of dry mouth among our trial was likely the unexpected OB effect on the salivary glands. Antimuscarinic drugs used to treat overactive bladder are occasionally associated with central nervous system side effects, eg, cognitive dysfunction, dizziness, fatigue etc.[35] Nausea and dizziness reported under OB treatment were suggested to result from the central antimuscarinic effect. However, other trials did not report these side effects.

The limitation of our OB study has been the single center and small-scaled trial. Usually, the small-scaled study may have inadequate sample size and study power to achieve an expected result, whereas single center trial sometimes leads to study bias.[36] Clinically, functional GI disordered subjects are often not very satisfactory to the recommended treatments because of the associated somatic complaints, functional disturbances existed in other organ systems, psychiatric disorders and social impacts.[2,3,13,37] Our enrolled subjects almost had consumed rescue agents during the trial. It is likely that they were very to concerned about the abnormal BM and had no confidence in relieving the abnormal BM activity even been informed of an active treatment. Since this is the first OB trial conducted in Asia, it remains uncertain whether OB could achieve an ideal efficacy to treat IBS patients comparable to that of European study.[17] Concerning its major antimuscarininc side effects, a large-scaled trial and post-marketing surveillance are recommended based on our preliminary results. In conclusions, OB effectively improved the IBS symptoms in terms of abdominal pain, flatulence, abdominal bloating, satisfied stool frequency and global assessment in Asian patients. Unfortunately, obvious side effects like dry mouth, nausea and dizziness were also observed. A large-scaled trial and post-marketing surveillance are recommended to confirm its true efficacy and safety.

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