Novel approach in the treatment of IBS

In a dinner symposium held at the Crowne Plaza Manila Galleria Hotel last March 12, 2013, Professor Pere Clavé talked about the benefits of otilonium bromide (Spasmonem®), Menarini and its role in the treatment of irritable bowel syndrome. Professor Clavé discussed the superiority of otilonium bromide to placebo in reducing the frequency of abdominal pain and symptom relapse. It is ideal for long-term treatment due to lack of anticholinergic activity and its excellent safety profile.

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder with high prevalence. Worldwide, about 16% to 21% of adults and adolescents have symptoms consistent with IBS. Most studies found a female predominance and symptoms come and go over time. As such, it impacts the quality of life and results in high health care costs. IBS is characterized by abdominal pain or discomfort with associated changes in bowel habit or problems in defecation. It can manifest with both gastrointestinal and extraintestinal complaints.

The Rome III criteria defined IBS as recurrent abdominal pain or discomfort associated with altered defecation. To diagnose IBS using Rome III, there should be recurrent abdominal pain or discomfort (uncomfortable sensation not described as pain) at least 3 days per month in the last 3 months. It should be associated with two or more of the following features: improved with defecation, onset that is associated with change in frequency of stool or onset associated with change in appearance (form) of stool. Symptom onset should be at least 6 months prior to the diagnosis.

Otilonium bromide (OB, Spasmonem®) is a spasmyloytic compound from a family of quaternary ammonium derivatives. OB works by inhibiting the main patterns of human sigmoid motility. It blocks calcium influx in L-type calcium channels in smooth muscle cells. OB has been shown to block 89% of non-neuronal rhythmic phasic contractions, as well as on- and off-contractions from excitatory motor neurons. OB also blocked acetylcholine, substance P, and neurokinin A-induced contractions. The drug is not absorbed systemically as observed in radiolabelling studies. It is eliminated mostly through the feces (97.8%) and accumulates specifically in the colonic circular muscle and not in other types of smooth muscle. Plasma levels are a thousand times lower than in colonic muscle. This property of OB makes extraintestinal adverse events unlikely.

Various factors are involved in the pathogenesis of IBS. Impaired motility has been seen in some patients, which might increase frequency and irregularity of luminal contractions. In constipation-predominant IBS patients, prolonged transit time was observed. In diarrhoea-predominant IBS, there is exaggerated motor response to cholecystokinin with meal ingestion, resulting in loose stools. Aside from impaired motility, hypersensitivity to stimuli was also proposed as a factor in its pathogenesis. Some patients have defective transit of intestinal gas loads. IBS patients experienced pain at lower balloon volumes when the rectosigmoid was distended compared to controls. Psychosocial factors are also associated with IBS. In one study, at increased incidence of anxiety, depression, phobias and somatization were seen in IBS patients but not with controls. Anxiety, sleep problems and somatic symptoms were proposed as risk factors for IBS development because some patients develop IBS symptoms after psychosocial stress.

There is no agreement over the optimal pharmacological treatment that fits all IBS patients. Since IBS is a chronic condition with no known cure, treatment should address the main symptoms of IBS that fits all IBS patients. Since IBS is a chronic condition with no known cure, treatment should address the main symptoms of IBS. Since IBS is a chronic condition with no known cure, treatment should address the main symptoms of IBS. Since IBS is a chronic condition with no known cure, treatment should address the main symptoms of IBS. Since IBS is a chronic condition with no known cure, treatment should address the main symptoms of IBS.

Since IBS is a diagnosis of exclusion, some practitioners are not comfortable with making a diagnosis. However, IBS is a legitimate diagnosis, and the likelihood of another organic diagnosis coming out is only 1% to 4% after 6 months to 6 years of follow-up.10 This assumes the Rome III criteria were met, the findings were well-documented and other organic etiologies had been reasonably ruled out when the diagnosis was made. In a Swedish survey, more than half of those with IBS reported the same symptom profile after 1 year and 7 years of follow-up (Figure 1).12 The prevalence of IBS increased over time in respondents, indicating the persistence of IBS even after 7 years.

For a patient to be included, he or she should be at least 18 years of age and have been diagnosed with IBS using the Rome III criteria. Patients also had to have episodes of abdominal pain per week during 2 weeks of run-in (severe IBS). The study had three phases: run-in phase, treatment phase and follow-up phase. In the run-in phase, patients were screened for inclusion in the study and given placebo TID for 2 weeks. In the treatment phase, 378 patients were given OB and 377 patients were given placebo for 15 weeks. In the follow-up phase, no treatment was given but observation for relapse and other factors was done for 30 weeks.

Otolonium Bromide in Irritable Bowel Syndrome (OBIS) study is a double-blind, randomized, parallel-placebo-controlled IV study that enrolled 556 patients and aimed to know the efficacy of OB for symptom control. Its primary endpoint was to determine the change in frequency of abdominal pain that OB can produce. It also aimed to know the effect of OB on other IBS symptoms, the change in relapse rates, as well as safety and quality of life (QOL). OBIS was an international study that involved both sexes in eight European countries.

The frequency of abdominal pain and the symptom relapse rates were significantly lower in OB compared to placebo. OB was significantly better than placebo in the follow-up phase for global efficacy scores from both the patients’ and investigators’ opinions. OB patients even had higher probability to be relapse-free than the placebo group (Figure 3). Withdrawal rate due to symptom relapse was significantly higher in the placebo group compared with the OB group.

OB has an excellent safety profile. The aforementioned in vitro data of OB suggested that it lacks anticholinergic activity with low systemic absorption.11 In the OBIS study, the most common adverse effects (ie, abdominal pain, diarrhea, flatulence and nausea) observed were minimal.13 The number of patients with adverse effects from OB and placebo were not significantly different. No patients withdrew from the trial due to adverse events in the OB group.

Summary

IBS is a common and underdiagnosed disorder with a great emotional and financial impact on patients. As a chronic and relapsing disorder, it significantly affects QOL. Otolonium bromide is recommended for treatment of IBS because it reduces abdominal pain frequency, severity of abdominal distension and symptom relapse. OB has a strong spasmyloytic activity, and is associated with low a incidence of adverse events due to its lack of anticholinergic activity and very low systemic absorption. Patients with IBS can improve during and following treatment with OB, which is recommended for long-term treatment of IBS to prevent relapse.

References