The use of anti-spasmodics in the treatment of irritable bowel syndrome: focus on otilonium bromide

F. FORTE, M. PIZZOFERRATO, L. LOPETUSO, F. SCALDAFERRI

Department of Internal Medicine, Division of Gastroenterology, School of Medicine, Catholic University of the Sacred Heart, Rome (Italy)

Abstract. – Objective: Aim of this review is to summarize the studies carried out, with particular interest in those who dealt with otilonium bromide, in treatment of IBS (Irritable Bowel Syndrome).

Discussion: IBS is a frequent gastrointestinal disease, characterized by a combination of several symptoms including abdominal pain or discomfort, flatulence and problems related to bowel habits (constipation and/or diarrhea). It affects about 15% of the western population, with a negative impact on the quality of life and also on healthcare costs. In relation to such important complexity and negative impact, therapeutic options are still very limited and most of the pharmacological compounds, validated for short term use, are only partially controlling symptoms. Among those, anti-spasmodics are commonly used in clinical settings. Despite a discrete literature in support of these drugs, systematic collections of clinical evidence to support the use of anti-spasmodics and in particular the use of otilonium bromide in course of IBS are scarce.

Results and Conclusions: Otilonium bromide is a systemically poorly absorbed antispasmodic, which has shown clear efficacy compared to placebo, in controlling symptoms related to IBS. Otilonium bromide was effective also in comparison to other drugs, such as pinaverium bromide and mebeverine, with a favorable tolerability profile. Further studies are necessary to better define duration of treatment and maximum therapeutic dose.

Key Words: Irritable bowel syndrome, Anti-spasmodics, Otilonium bromide.

Introduction

Irritable bowel syndrome (IBS) represents the most frequently encountered functional digestive disorder in gastroenterology practice. It is characterized by an inconstant association of symptoms like abdominal pain or discomfort associated with disorders of bowel movement (constipation or diarrhea) and/or symptoms such as bloating and abdominal distension. The social impact of this disease is significantly high, with important limitation in quality of life and productivity, increased absenteeism from work and relevant costs for health systems because of repetitive diagnostic test and therapies. IBS is a complex disease, in which the wide range of symptoms cannot be always attributed to the numerous pathological mechanisms hypothesized. That is the main reason of the lacking of an appropriate specific etiologic therapy.

Epidemiology and Pathogenesis of IBS

Precise estimation of IBS epidemiology is complex due to several reasons: the variety of factors involved in its pathogenesis, the diagnostic difficulties due to the absence of specific and reproducible examinations or markers, the variety of used criteria, the variability of clinical manifestations as well as the division of medical management in self-medication (71-80%), family medicine (20-29%) and referral centers (1%), in the absence of a common database. Despite this, it is commonly recognized that IBS is a widespread disease, with high prevalence in western countries and in women (M/F 1:2) varying from 2.5%, when considering only 1 of the 6 Manning’s criteria described below, to 37% adopting all 6 criteria or 10% with 3 criteria. It is generally accepted, however, that IBS affects 10-15% of western population. Historically IBS has been considered a functional issue, without any clear evidence of anatomical or metabolic or inflammatory or infectious damage.
so involving primarily a distorted perception and processing of pain. Modern understandings are considering IBS as a multifactorial disease, where genetic factors, inflammatory changes caused by gastrointestinal infections, nutrition, and psychosocial aspects play a crucial role[1-3]. In this complex system of events, gastrointestinal motility disorders also play a role, determining an exaggerated response to the ingestion of food and/or stressful events[1].

It seems clear, nowadays, that patients with diarrhea have an increased intestinal motility and accelerated bowel transit, while those with constipation display reduced motility and bowel transit[1]. Furthermore, IBS patients seem to display visceral hypersensitivity, which consists in increased sensitivity to mechanical stimulation of the bowel, alteration observed in approximately 2/3 of IBS patients[1]. The involvement of central and peripheral mechanisms can also support the presence of a chronic pain in IBS patients[1].

Food allergy diagnosis (prevalence < 1-2%) excludes by definition the diagnosis of IBS. Some studies, on the contrary, support the role of food intolerance in IBS pathogenesis, although methods for intolerance evaluation are not always correct. Among food intolerance, lactose intolerance plays a possible important role in IBS pathogenesis. Various types of stress predispose IBS and facilitate the onset of symptoms in children through the activation of pituitary-adrenal axis or pituitary disorders, mediated by corticotrophin release factor (CRF), the hypothalamic stress hormone responsible for behavioral, autonomic, immune and visceral stress events. IBS patients display an increased response to stress with a high production of CRF[8-10]. Upon CRF release[11,12], Substance P (SP) and Peptide Related to the Gene of Calcitonin (PRGC)[13,14] are released and are responsible to an increase in intestinal permeability, greater bacterial adhesion to the mucosa and increased bacterial translocation to the spleen[15]. At morphological level both in rats and humans there is a load of mitochondrial swelling enterocytes, infiltration immune, mucous depletion and degranulation of mast cells[16,17]. These changes persist in the animal even after removal of the stressful factor because of the ability of mast cells to change their interaction with neurons[14,18]. The same effects have been observed in humans[19,20]. A bidirectional synergism stress-inflammation can further sustain these disorders. In fact, it is generally agreed that micro-inflammation plays an important role in IBS pathogenesis, sustaining the vicious circle of immune activation – altered response to stress and inflammation. Low grade intestinal inflammation in IBS patients, and in particular the activation of neurons mediated by the release of tryptase from mast cell, could be responsible of visceral hypersensitivity through the direct activation of trans membrane protein called neuronal receptors-2 activated by proteinase (PAR2). That could be one of the possible mechanisms responsible for alteration in pain perception[21,22] as well as induction of chronic pain[23,24] in IBS patients. Furthermore, IBS patients seem to display a hyperactivity of posterior horns of spinal cord which could also be responsible for lower extremities skin hyperalgesia, because of the convergence of nociceptive inputs of lower extremities with visceral somatic ones[21,25,26]. Micro-inflammation could also influence serotonin pathways.

Serotonin can directly affect gastrointestinal motility and sensitivity through its 7 receptor subtypes, which can be found in the brain as well as in enterochromaffin gastrointestinal cells[27]. IBS patients, particularly diarrhea type, have been shown to display an increased number of enterochromaffin cells which produce serotonin following intestinal micro-inflammation; that is the main reason of the use of tegaserod, partial agonist 5HT4, in IBS with constipation or alos-teron antagonist 5HT3, in the variety with diarrhea. To make the situation more complicated there is the fact that in IBS patients a reduction in proteins for serotonin reuptake further extends the effect of serotonin[27,28].

Intestinal micro-inflammation is probably maintained by intestinal antigenic factors such as food, bacteria, fungi in the presence of increased intestinal permeability at least partly related to the activation of PAR2, responsible for the tight junctions alteration and mast cells alterations. It has been shown that probiotics and prebiotics can actively act on these mechanisms, partially controlling IBS related symptoms[29,30].

IBS adults and children display an altered intestinal microflora compared to general population, probably the result of incorrect eating habits or prolonged antibiotic therapy.

More than 60% of IBS patients recognize in certain type of foods the triggering event of symptoms while elimination of certain foods in some studies has shown efficacy in reducing symptoms[32]. However, despite these reports, despite the efficacy of disodium chromoglyc ate that
inhibits the degranulation of mast cells, there are still many doubts about the real role of elimination diets in treating IBS.

Finally, another important cause of symptoms in IBS is small intestine bacterial overgrowth (SIBO). This condition could be caused by several IBS symptoms including bloating, pain and could evoke an inflammatory response through more complex neuro-endocrine-immunological local alterations.

The complex relationships of all these factors and mechanisms described above can be summarised in a pathogenic model of IBS that currently remains a fascinating working hypothesis.

Clinical Symptoms as Cornerstone in the Diagnosis of IBS

Main problems related to IBS management are represented by the diagnostic accuracy and precise definition. IBS could be classified on the base of bowel symptoms in diarrhea (D) type, constipation (C) type and mixed (M) diarrhea and constipation type.

First attempts to define the diagnostic criteria for irritable bowel syndrome date back to 1970 and to the work of Manning et al (Table I).

Subsequently, a more precise definition of IBS and more valid diagnostic criteria, from Rome 1990 criteria to Rome II criteria in 1999, have been developed. The most recent Rome III criteria shown in Table II, elaborated in 2006, have changed only slightly previous documents.

Crucial symptom for IBS is pain, or abdominal “discomfort”, clearly related to intestinal function, which is typically relieved by defecation (suggesting an origin from colon) or associated with changes in the form of stool (thus suggesting a correlation with intestinal transit). Frequent symptoms in irritable bowel syndrome, but not included in the diagnostic criteria are: bloating, anomalies in the form of feces, increase in the number of evacuations, effort during defecation, urgency of stimulus, sense of incomplete evacuation and expulsion of mucus in the feces.

The late or sometimes not done IBS diagnosis or incorrect management of patients with irritable bowel syndrome has a huge impact on health care spending with an annual cost per patient extremely higher than comparable subjects without disease. For example, a survey from US on the costs of medical care delivered on an outpatient basis showed an annual cost of US $ 4,000 for an IBS patient and of US $ 2,700 for a control, determining a difference of 49%. IBS absorbs around the 28% of the consultations in gastroenterology and represents 12% of those realised on an outpatient basis. It has been estimated that in 1998 3.65 million gastroenterological visits for irritable bowel syndrome have been carried out.

The irritable bowel syndrome has strong social-economic impact in that consumption of health care resources are accompanied by the lack of work, and the low quality of life. It has been calculated that in a year the absences from work among the subjects with irritable bowel syndrome are three times those of corresponding controls: 13.4 to 4.9 days. An important element that contributes to the high medical expenditure in patients with irritable bowel syndrome is represented by co-morbidity: in fact these patients consult a doctor for a large quantity of symptoms, either related to the gastrointestinal tract or not.

Patients with irritable bowel syndrome undergo medical examinations twice as compared to controls and 78% of visits in most were not related to gastric disease. Co-morbidity tends to be more marked in relation to psychiatric diagnosis: in any case, the mental disorder influences but does not explain the co-morbidity.

**Table I.** Manning’s criteria for the diagnosis of irritable bowel syndrome. (Adapted from Spiller R et al).

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>Pain relieved by defecation</td>
</tr>
<tr>
<td>2</td>
<td>Evacuations more frequent at the onset of pain</td>
</tr>
<tr>
<td>3</td>
<td>Soft feces before the onset of pain</td>
</tr>
<tr>
<td>4</td>
<td>Evident abdominal distension</td>
</tr>
<tr>
<td>5</td>
<td>Emission of mucus from anus</td>
</tr>
<tr>
<td>6</td>
<td>Sense of incomplete evacuation</td>
</tr>
</tbody>
</table>

**Table II.** Criteria Rome III for the diagnosis of irritable bowel syndrome. (Adapted from Spiller R et al).

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>Abdominal pain or discomfort applicant for at least 3 days a month in the last 3 months, associated with 2 or more of these factors:</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>• Improvement with defecation</td>
<td></td>
</tr>
<tr>
<td>• Occurrence associated with a change in the frequency of evacuations</td>
<td></td>
</tr>
<tr>
<td>• Occurrence associated with a change in the appearance (shape) of faeces</td>
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</table>

Criteria satisfied in the last 3 months with the onset of symptoms at least 6 months before the diagnosis.

Discomfort means an unpleasant sensation, not definable as pain.
**Therapeutic Approach in Irritable Bowel Syndrome (IBS)**

The need for effective therapy in the management of irritable bowel syndrome is an absolute priority for modern gastroenterology. However, the complex pathogenesis, the complex diagnostic definition and the lack of a specific pathway are shared by various forms of irritable bowel and make the identification of pharmacological targets very difficult.

Symptomatic treatment represents today the main target of pharmacological therapy, for both the abdominal pain and the altered intestinal transit (constipation, diarrhea), and, on reflection, for the consequences of the latter, such as flatulence and incontinence. The therapeutic approach must take into account the intensity of the symptoms, the size of the medical intervention and the degree of associated psychosocial diseases. The treatment must be based on reassurance, education and modification of diet and lifestyle, as well, of course, on the appropriate pharmacotherapy.

The pharmaceutical categories today routinely used in the management of IBS include antispasmodics, prokinetics, alrosetron, tegaseron antidepressants, antibiotics, prebiotics and intestinal anti-inflammatory agents. Among these, antidepressants are especially effective in IBS patients of the diarrhea type. Tegaseron and alrosetron are mainly effective in the female population, the first is used in constipation variant and the second in the diarrheal. The loperamide may be used in the treatment of irritable bowel syndrome in patients without abdominal pain and with diarrhea.

**Anti-spasmodics Medicines for the Treatment of Irritable Bowel Syndrome (IBS)**

This paper will present a review of clinical trials and meta-analyses which are judged to be of high quality on the use of anti-spasmodics, compared to placebo or other drugs. At the end of this review, a possible use will be proposed, based on the evidence, of the various classes of drugs studied in specific clinical conditions.

The first meta-analysis of randomized studies on the efficacy of antispasmodics in the treatment of IBS patients was conducted by Poynard et al and published in 1994. In this meta-analysis 5 active drugs were identified as being without significant side effects: cimetropium bromide, pinaverium bromide, trimebutine, otilonium bromide, mebeverine.

Subsequently, a second more recent meta-analysis was published in 2002 by Poynard et al, highlighting 6 active drugs without significant side effects. In this study the Authors have considered only randomised double-blind, placebo-controlled studies, published as extended work. Total number of patients treated accounted approximately to 1888 while 943 patients received placebo. Main endpoint was represented by clinical improvement, as reported in Table III.

Results demonstrated the therapeutic value of antispasmodics in pharmacological treatment of IBS patients, with Odd’s ratio and risk reduction significantly in favor of active treatment compared to placebo (Table IV).

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**Table III.** Main features of meta-analysis of Poynard et al on the effectiveness of antispasmodics. (Adapted from Poynard T, et al) 40.

<table>
<thead>
<tr>
<th>Design studies</th>
<th>Randomized, double-blind, placebo-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies evaluated</td>
<td>23</td>
</tr>
<tr>
<td>Type of studies</td>
<td>Clinical, published as articles (no abstracts or letters)</td>
</tr>
<tr>
<td>Period of publication</td>
<td>Since 1965 (mebeverine) and 1999 (otilonium bromide)</td>
</tr>
<tr>
<td>Main endpoint</td>
<td>Overall improvement</td>
</tr>
<tr>
<td>Other endpoints</td>
<td>Improvement of abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Improvement of constipation</td>
</tr>
<tr>
<td></td>
<td>Improvement of intestinal transit</td>
</tr>
<tr>
<td></td>
<td>Improvement of abdominal distension</td>
</tr>
<tr>
<td></td>
<td>% of patients without side effects</td>
</tr>
<tr>
<td>Assessment</td>
<td>Qualitative and quantitative</td>
</tr>
<tr>
<td>Treatments considered</td>
<td>Antispasmodics without significant side effects</td>
</tr>
<tr>
<td>Drugs considered</td>
<td>Cimetropium bromide (5 studies) mebeverine (5 studies) otilonium bromide (4 studies), trimebutine (4 studies) hyoscine 0.1 mg butylbromide (3 studies), pinaverium bromide (2 studies)</td>
</tr>
<tr>
<td>Casuistry</td>
<td>At least 51% of patients with IBS in each study</td>
</tr>
<tr>
<td>Patients</td>
<td>1888 (active drug) 943 (placebo)</td>
</tr>
</tbody>
</table>
Considering separately each drug, a remarkable variability in clinical response could be observed, in particular, in relation to the parameters of overall effectiveness (range of response from 31% to 11%) and control of pain. Although a direct comparison between the various drugs is not possible and it is not the main objective of the proposed meta-analyses, it could be observed that otilonium bromide was particularly effective when compared to placebo, in the resolution of symptoms (Figures 1, 2).

**Otilonium Bromide in the Treatment of Irritable Bowel Syndrome (IBS)**

The first study which demonstrated the efficacy of otilonium bromide in patients with IBS, diarrheic variant, is that of Battaglia et al., evaluating a wide Italian population.

In this randomized, double-blind, placebo-controlled parallel-group study, conducted in 23 Italian Centers, 378 IBS patients (121 males and 257 females) were enrolled. The treatment was provided for 15 weeks with otilonium bromide 40 mg tid or placebo, with controls at 5, 10 and 15 weeks. The evaluation of the efficacy was based on three main symptoms (abdominal pain, abdominal distension, disorders in the defecation), and to each of them a score was assigned. Abdominal pain was measured in frequency (number of episodes: none, 3 or more, from 4 to 7) and intensity (absent, mild-to-moderate, severe and very severe); overall score was calculated by multiplying frequency for the intensity. A similar calculation applied to abdominal distension. The treatment success was defined as the reduction from baseline in at least one unit of scores.

Admission to 15 weeks of treatment was reached for 325 patients (100 males and 225 females), 160 of which received otilonium bromide and 165 placebo. Results showed that treatment with otilonium bromide significantly reduced abdominal pain (frequency of episodes) at 10 and 15 weeks ($p < 0.05$ and $< 0.001$, respectively) compared with the placebo treatment (Figure 3).

In the study, the reduction in the overall score of abdominal pain was significantly in favor of otilonium bromide, as shown in Figure 4.

Number of patients with reduced frequency of abdominal pain was greater in the group treated with otilonium bromide compared to placebo, with statistically significant differences ($p < 0.01$) (Odd’s ratio 1.87, 95% CI 1.20-2.91) (Figure 5).

Considering abdominal pain, the success of therapy was significantly more frequent in group of patients treated with otilonium bromide compared to placebo ($p < 0.05$) (Odd’s ratio 1.67, 95% CI 1.05-2.65) (Figure 6).

Otilonium bromide exerted a favorable effect in the management of several physical signs associated to IBS, as the tenderness of the colon and other parameters reported in Figure 7.

Finally, the improvement of the well-being state and the judgment of the investigator significantly favored otilonium bromide versus placebo ($p < 0.01$ and $p < 0.05$, respectively) (Figure 8).

Recently (2011), the results of a multicentre (34 Centres), double-blind, randomized, parallel-

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**Table IV.** Results of meta-analysis of Poynard et al on effectiveness of antispasmodics in the global population. (Adapted from Poynard T, et al).

<table>
<thead>
<tr>
<th>Studies included</th>
<th>21</th>
</tr>
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<tbody>
<tr>
<td>Overall improvement</td>
<td>56% active drugs (n = 927) 38% placebo (n = 925)</td>
</tr>
<tr>
<td>% patients</td>
<td>2.13 ($p &lt; 0.001$, 95% CI 1.77-2.58)</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>22% ($p &lt; 0.001$, 95% CI 13-32)</td>
</tr>
<tr>
<td>Significant differences in favor of active drugs</td>
<td></td>
</tr>
<tr>
<td>Improvement in pain</td>
<td>53% active drugs (n = 567) 41% placebo (n = 568)</td>
</tr>
<tr>
<td>% patients</td>
<td>1.65 ($p &lt; 0.001$, 95% CI 1.30-2.10)</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>18% ($p &lt; 0.001$, 95% CI 7-28)</td>
</tr>
<tr>
<td>Significant differences in favor of active drugs</td>
<td></td>
</tr>
<tr>
<td>Improvement of abdominal distension</td>
<td>44% active drugs (n = 442) 35% placebo (n = 443)</td>
</tr>
<tr>
<td>% patients</td>
<td>1.46 ($p &lt; 0.001$, 95% CI 1.30-2.10)</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>18% ($p &lt; 0.001$, 95% CI 7-28)</td>
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<tr>
<td>Significant differences in favor of active drugs</td>
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</table>
Figure 1. Meta-analysis of 21 studies on the effectiveness of antispasmodics in the treatment of IBS patients: results expressed as percentage of patients with overall improvement. (Adapted from Poynard T, et al).
The use of anti-spasmodics in the treatment of irritable bowel syndrome

Patients who completed the 15-week scheduled period were subsequently allocated to a 10-week follow-up, without receiving any drug therapy.

At the end of the treatment, statistically significant differences were observed in favour of otilonium bromide versus placebo for both, the primary endpoint (frequency of abdominal pain episodes) and two secondary endpoints (bloating

![Figure 2. Meta-analysis of 21 studies on the effectiveness of antispasmodics in the treatment of IBS patients: results expressed as percentage of patients with improvement of abdominal pain. (Adapted from Poynard T, et al)](image-url)
Figure 3. The frequency of abdominal pain: changes in the score in the 2 treatment groups, otilonium bromide 40 mg tid or placebo. (Adapted from Battaglia G, et al).

Figure 4. Reduction in the overall score of abdominal pain in the 2 treatment groups, otilonium bromide 40 mg tid or placebo. (Adapted from Battaglia G, et al).

F. Forte, M. Pizzoferrato, L. Lopetuso, F. Scaldaferrì demonstrated the efficacy of otilonium bromide in symptom control in patients with irritable bowel syndrome41.

Furthermore, the above study suggests that the effect of otilonium bromide can persist even after discontinuation of this drug41. More precisely, there was evidence that the results obtained with otilonium bromide at the end of the treatment period, as for reduction of abdominal pain, were long lasting, persisting also during the follow-up. In fact, it has been reported in the placebo group a high incidence of withdrawals, due to symptom recurrences, with statistically significant differences in comparison with otilonium bromide: 27% versus 10%, p = 0.0089. Similarly, the probability for the patient to stay symptom-free in the post-treatment phase was significantly higher in the otilonium bromide group versus placebo (Figure 9)41.

As a concluding remark, it is worthy to notice that the persistence of the effect of otilonium bromide after its withdrawal, can be of major importance in clinical management of IBS, particularly when adopting an intermittent drug regimen41.

In conclusion, clinical trials of otilonium bromide4,42,43 and meta-analyses described above3,39,40 have shown a good efficacy of this drug versus placebo in the treatment of IBS, with significant differences on many endpoints.

Otilonium bromide resulted effective not only against placebo but also toward some other treatments44,45. Although the most frequent dietary advices suggest to patients with IBS to adopt diets rich in fibers, there is no evidence of their real severity and patient assessment of global efficacy) (Table V).

These data generally confirm what already observed in previous clinical studies, which demonstrated the efficacy of otilonium bromide in symptom control in patients with irritable bowel syndrome41.
beneficial effects\textsuperscript{1}. Indeed, a search in this sense, pointed out that a high fiber content of cereals may also be associated with a worsening of symptoms in 55\% of cases\textsuperscript{1}.

In 114 patients with irritable bowel syndrome, otilonium bromide 40 mg tid (n = 61) was more effective than a diet that included daily 20 g of fiber and 10 g of bran (n = 53)\textsuperscript{44}. The drug has led to an improvement in pain and abdominal distension toward pre-treatment significantly higher respect to the results of the diet alone at the end of 24 months of follow-up (p < 0.01)\textsuperscript{44}.

In 40 patients with irritable bowel syndrome, otilonium bromide displayed significant improvement in symptoms compared to pinaverium bromide\textsuperscript{45}. Otilonium bromide (20 mg tid) resulted equally effective to cimetropium bromide (50 mg bid), in double-blind evaluation for the period

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**Figure 5.** Number of patients with reduced abdominal pain intensity in two groups: otilonium bromide 40 mg tid vs placebo. (Adapted from Battaglia G, et al\textsuperscript{1}).

**Figure 6.** Efficacy of therapy: reduction of symptoms score in two groups: otilonium bromide 40 mg tid vs placebo. (Adapted from Battaglia G, et al\textsuperscript{1}).

**Figure 7.** Otilonium bromide efficacy in reducing IBS physical signs in two groups: otilonium bromide 40 mg tid vs placebo. (Adapted from Battaglia G, et al\textsuperscript{1}).
of 6 weeks on 40 patients with irritable bowel syndrome.

Both treatments resulted in a significant reduction in the severity of abdominal pain and of scores assigned to bowel habits. Two important aspects must be emphasized: first of all, the cimetropium bromide is an antispasmodic highly active and secondly in this study otilonium bromide was used at a particularly low dose, about half compared to that normally adopted i.e. 40 mg tid.

The association of otilonium bromide and benzodiazepines such as diazepam, may represent a useful alternative to the use of antispasmodics in monotherapy, as they can further improve the beneficial effects of the drug on gastrointestinal system by controlling anxiety.

The clinical effectiveness of otilonium bromide can be determined by several mechanisms of action, determined by the presence of several receptors and chemical mediators.

Otilonium bromide is a chemical product composed by quaternary ammonium, a compound with direct antispasmodic action on distal gastrointestinal tract. The drug is also able to act on cholinergic pathways, neurokines receptors and calcium channels, leading to an efficient muscular relaxation, resulting in effects on intestinal motility, pain perception and visceral sensitivity.

More precisely otilonium bromide counteracts muscarinic receptors, including those for the acetylcholine, blocking the stimulating action of this transmitter. Otilonium bromide acts on the calcium channels, by modifying the flows from intra- and extra-cellular deposits at the level of abdominal smooth muscle. Otilonium bromide inhibits, in addition, tachichinine receptors and neurochines involved in motility and intestinal algesia.

Otilonium bromide enhances, finally, the threshold of sensitivity to detente rectum-sigmoidian. Otilonium bromide is poorly absorbed systemically: acts, therefore, mainly at local level without sig-

**Figure 8.** Comparison between otilonium bromide 40 mg tid and placebo in improving well-being status (10-point VAS) and physician rating of effectiveness. (Adapted from Battaglia G, et al.).

**Table V.** Efficacy of otilonium bromide versus placebo in 365 patients with irritable bowel syndrome: results at the end of 15-week treatment. (Adapted from Clavé P et al.).

<table>
<thead>
<tr>
<th></th>
<th>Reduction of abdominal pain frequency</th>
<th>Reduction of bloating severity</th>
<th>Patient assessment of global efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otilonium bromide 40 mg tid</td>
<td>$-0.90 \pm 0.88$</td>
<td>$-1.20 \pm 1.20$</td>
<td>$1.13 \pm 1.20$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-0.65 \pm 0.90$</td>
<td>$-0.90 \pm 1.10$</td>
<td>$0.90 \pm 1.10$</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>$p = 0.038$</td>
<td>$p = 0.02$</td>
<td>$p = 0.047$</td>
</tr>
</tbody>
</table>

**Figure 9.** Impact of otilonium bromide on the probability for the patient to be free from long-term recurrences of symptoms: results of the 10 weeks of follow-up after the 15 weeks of treatment. (Adapted from Clavé P, et al).
significant side effects. In a recent review on tolerability and safety of drugs currently in use in IBS treatment, it has been emphasized the lack of information about drugs metabolism for the majority of pharmacological treatments, while there is no shortage of information about the evaluations of effectiveness. In order to go deeper in these data, our systematic review is meant to be carried out in the literature according to strict criteria, highlighting for otilonium bromide a satisfactory tolerability profile. Almost no side effects were associated to the use of this drug: two reports did not reveal any adverse effect, while another reported one case of mild nausea.

In another research otilonium bromide was compared to pinaverium bromide. Monitoring of side effects showed a better outcome for otilonium bromide treatment with 0.8 adverse effects for year-patient toward the 2.5 of comparator. In another study controlled with placebo, 3 suspensions of treatment were detected, 1 with placebo and 2 with otilonium bromide. Data from safety and post-marketing observation, showed that otilonium bromide is well tolerated, and side effects do not differ with placebo. Finally, 10 years post-marketing surveillance reported only two adverse reactions (urticaria).

Conclusions

The irritable bowel syndrome is a very complex pathological condition, for which there is no unified management nationally or internationally. Cornerstone of diagnosis and therapy for IBS are symptoms, mostly related to pain/discomfort and alteration of bowel motion. Various medications are used for clinical management of this condition, however no studies are able to stratify patients depending on their response to therapy or need for a specific drug. Clinical research, in fact, still needs to meet this goal.

Anti-spasmodics are a pharmacologic category generally used in course of IBS, with a good safety profile, and good data regarding effectiveness in the treatment of diarrhea/IBS. Among these, otilonium bromide stands out for handling and effectiveness.

More efforts should be put into the research of diagnostic, prognostic and pharmacological approaches to make a better quality of life for IBS patients.

References


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