Abstract. – Objective: To investigate the efficacy and tolerability of octatropine methyl bromide plus diazepam (Valpinax®) in patients with irritable bowel syndrome (IBS).

Materials and Methods: We conducted a randomized, double-blind, multicentre study in 186 patients aged 18-65 years with IBS diagnosed according to Rome II criteria. Following a 2-week washout period, patients received octatropine plus diazepam 40 mg/2.5 mg twice daily or placebo for 6 weeks. The primary efficacy endpoint was response to a weekly question: “did you have satisfactory relief of your abdominal pain and discomfort during the last week?” Other endpoints included abdominal swelling, abdominal pain and discomfort, symptom severity, and the number of bowel movements. A prespecified subgroup analysis was conducted in patients with an abdominal pain and discomfort score ≥3.

Results: The primary efficacy endpoint showed a tendency towards a statistically significant benefit for octatropine plus diazepam over placebo among patients with a baseline abdominal pain and discomfort score of ≥3 (3 vs. 0 patients; p = 0.059). Octatropine plus diazepam demonstrated significant improvements from baseline in all parameters assessed, but not compared with placebo. Adverse events were reported in 15.1% of patients receiving octatropine plus diazepam.

Conclusions: Patients with IBS and an abdominal pain and discomfort score of ≥3, who may be considered in the active phase of the disease, may derive some benefits from octatropine plus diazepam. This study highlights that Rome II criteria should be considered with particular care in the design of a clinical trial, since it does not consider disease activity level on admission.

Key Words: Diazepam, Irritable bowel syndrome, Octatropine; Tropanes.

Introduction

The term irritable bowel syndrome (IBS) refer to a well recognized complex of symptoms arising from interactions of the intestine, the psyche and, possibly, luminal factors. IBS is a disorder characterized by cramping, abdominal pain, bloating, constipation, and diarrhoea, and causes a great deal of discomfort and distress. As many as 20% of the adult population has symptoms of IBS, making it one of the most commonly diagnosed disorders. IBS is more common in women than in men and presents before the age of 35 in approximately 50% of those affected1-4. In most patients, symptoms can be controlled with diet, stress management, and prescribed medications. However, for some people IBS can be disabling. They may be unable to work, attend social events, or travel even short distances5-7.

Abdominal pain, bloating, and discomfort are the main symptoms of IBS. However, symptoms can vary from person to person and from time to
time. Some patients experience constipation or infrequent bowel movements. These patients frequently report straining and cramping when trying to have a bowel movement but either cannot eliminate stools or can eliminate only a small amount. If they are able to have a bowel movement, there may be mucus in it. Diarrhoea is also common among patients with IBS, resulting in frequent, loose and watery stools. Patients with diarrhoea frequently feel an urgent and uncontrollable need to have a bowel movement. The symptoms of IBS may subside for a few months at a time and then return, while some patients report a constant worsening of symptoms over time.

The specific cause for IBS is currently unclear and motility disorders of the gut have been proposed as the cause in the past. More recently, derangement of visceral sensitivity has been suggested. It has recently been reported that serotonin is linked with normal gastrointestinal (GI) functioning. The majority of serotonin in the body (95%) is located in the GI tract and the remaining 5% is found in the brain. Cells that line the inside of the bowel work as transporters and carry serotonin out of the GI tract. People with IBS, however, have diminished receptor activity, causing abnormal levels of serotonin to exist in the GI tract. As a result, patients with IBS experience problems with bowel movement, motility and sensation, having more sensitive pain receptors in their GI tract. In addition, people with IBS frequently suffer from depression and anxiety, which can worsen symptoms. Similarly, the symptoms associated with IBS can cause a person to feel depressed and anxious.

The usual treatment of IBS includes increased dietary fibre intake for constipation, loperamide for diarrhoea, and antispasmodics or low-dose antidepressants for pain relief. Nevertheless, the efficacy of some currently available treatment remains to be clearly established because of the poor design of clinical trials, such as lack of placebo control and double blinding.

Octatropine methyl bromide (octatropine) is a quaternary ammonium antimuscarinic agent that has been used for many years to relieve visceral spasm and is widely used in relieving the pain caused by smooth muscle spasm in IBS. Diazepam is a benzodiazepine with anxiolytic, sedative and muscle-relaxant properties. Octatropine in combination with diazepam (Valpinax®) is widely used in Italy for the treatment and relief of symptoms related to IBS. Previous studies have established the therapeutic efficacy of the octatropine plus diazepam combination product over octatropine and diazepam monotherapy in IBS patients.

The present study was designed to evaluate and confirm the clinical efficacy of the combination of octatropine and diazepam in patients suffering from IBS diagnosed according to the recent Rome II criteria.

Material and Methods

Study Design

This was a 6-week randomized, double-blind, parallel-group, placebo-controlled, multicenter study. The study was performed according to the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was designed according to EMEA guidelines for treatments for IBS and was approved by the Ethics Committees at all participating centres. All patients gave their written informed consent to participate in the study.

Patients

IBS outpatients aged between 18 and 65 years were recruited from 15 hospital centres in Italy. IBS had to be diagnosed more than one year before the recruitment. All patients were screened according to Rome II criteria for IBS. These are that patients had previously experienced abdominal discomfort/pain with two of the following characteristics: (a) relief with defecation; (b) onset associated with a change in stool frequency; or (c) onset associated with a change in stool form, for at least 12 weeks (not necessarily consecutive) during the previous 12 months. At baseline, IBS severity was evaluated using a 100 mm visual analogical scale and a score between 30 and 50 mm was required for inclusion in the study. Exclusion criteria were: chronic severe constipation with less than one stool per week; previous history of GI surgery (except appendectomy, cholecystectomy or hemorrhoidectomy); other GI diseases (except hemorrhoids and uncomplicated diverticula), as assessed by ultrasonography, colonoscopy or rectoscopy; a recent history of drug or alcohol abuse; intolerance to lactose; severe psychiatric disorders; aspartate aminotransferase or alanine aminotransferase greater than twice the upper limit of normal; use of other investigational drugs within three
months of the screening visit; and female patients not using adequate contraceptive precautions. Concomitant use of any medication that could affect GI motility was not permitted during the study. Limited use of laxatives such as glycerine, and diosmectite to treat diarrhoea, was allowed in rare cases and under the supervision of the investigator. Patients recorded every concomitant drug taken during the study period in their diary and were instructed to follow their usual diet, including any alimentary restriction.

**Study Protocol**

The study consisted of a 2-week wash-out period followed by a 6-week double-blind treatment period. Patients who met the inclusion criteria at control visit 1 entered a 2-week screening phase during which they received placebo and filled out a daily diary recording the severity of abdominal pain, number of evacuations, and stool consistency. At the baseline visit (week 0, control visit 2), patients were randomly allocated in a 1:1 ratio to receive treatment with octatropine/diazepam 40 mg/2.5 mg combination product twice-daily or placebo for 6 weeks with control visit 3 occurring in week 3 and visit 4 at the end of treatment week 6. Treatment numbers were assigned consecutively in ascending order. The randomization list, in blocks of 4, was generated by a computer system independently of the investigator and study sponsor. The codes were kept confidential until the end of the study. EMEA guidelines state that the patient’s global assessment of symptoms and abdominal discomfort should be used as endpoints in clinical trials in IBS18. In this study, the primary efficacy endpoint was therapeutic success, assessed by patients’ response to a weekly question: “did you have satisfactory relief of your abdominal pain and discomfort during the last week?” Other efficacy endpoints included abdominal swelling (measured with a digital scale: no = 0; very mild = 1; mild = 2; moderate = 3; severe = 4; very severe = 5), abdominal pain and discomfort (measured with a digital scale: no = 0; very mild = 1; mild = 2; moderate = 3; severe = 4; very severe = 5), and number of bowel movements per day. These were assessed on a daily basis by the patient noting results on a semiquantitative scale, different for each parameter, and discussing the daily diary with the investigator at each control visit.

A subgroup analysis was conducted in patients with an abdominal pain and discomfort of moderate or higher intensity (i.e. a score ≥3).

Tolerability was assessed at week 3 and 6 by evaluating the incidence and severity of reported adverse events, and the relationship of these adverse events to study medication.

**Statistical Analyses**

Between-group comparisons of endpoints were performed using Fisher’s exact test, Student t test, or Chi square test, where appropriate. Published literature for octatropine plus diazepam shows a success rate of 80% (95% confidence intervals 62.47-97.53). As a prudential rule, sample size calculation was done using the hypothesis of 70% success rate with octatropine plus diazepam and 50% with placebo. Using alfa 0.05 and beta 0.20, an estimated sample size of 103 patients per treatment group was required.

**Results**

**Patients**

A total of 206 patients were screened and the 186 patients who correctly completed daily diary records and provided consent entered the randomized treatment period. Of these, 16 patients (9 in the active group and 7 in the placebo group) discontinued the study prematurely (7 for consent withdrawal, 4 for adverse events or lack of compliance, 3 for loss at follow-up or protocol violation, and 2 for insufficient response). In total, 170 patients concluded the study and were considered for statistical analysis; 83 patients received octatropine plus diazepam and 87 patients received placebo. Patients’ disposition during the study is shown in Figure 1. There were no statistically significant differences at baseline among the two treatment groups for any of the key demographic features (Table I). In total, 10 patients (10.9%) in the active group and 14 patients (14.9%) in the placebo group had pain and discomfort of at least moderate intensity.

**Efficacy**

In total, 59 patients in the active group and 59 patients in the placebo group experienced therapeutic success, with no significant between-group difference seen. However, when only patients with pain and discomfort of at least moderate intensity were analyzed, there was a tendency towards significantly more patients receiving octatropine plus diazepam experiencing therapeutic success compared with placebo (p =0.059; Figure 2).
Abdominal swelling score (Figure 3) was significantly reduced at week 6 compared with baseline values in both groups (octatropine/diazepam 1.85 ± 1.02 at baseline vs. 1.30 ± 1.01 at week 6; placebo 1.72 ± 1.19 vs. 1.20 ± 1.08; both \( p < 0.001 \)). This reduction was already significant after three weeks (\( p < 0.05 \)), but no significant between-group differences were observed at either time point. Abdominal pain and discomfort was also significantly reduced at study end compared with baseline values in both groups (octatropine/diazepam 1.65 ± 0.95 at baseline vs. 1.19 ± 0.96 at week 6; placebo 1.60 ± 1.15 vs. 1.12 ± 1.01; both \( p < 0.005 \)) (Figure 4). The difference between week 3 and baseline was not statistically significant in either group, although a trend towards a reduction was evident. No significant between-group differences were observed.

The number of bowel movements was also reduced in both groups, although not significantly so, compared with baseline (octatropine/diazepam 1.24 ± 0.90 at baseline vs. 1.13 ± 0.70 at week 6; placebo 1.31 ± 0.97 vs. 1.25 ± 0.62).

The subgroup analysis conducted in patients with pain and discomfort of moderate, severe or very severe intensity showed that 6 weeks’ treatment with octatropine/diazepam resulted in a 43% reduction in the severity score compared with a 32% reduction in placebo recipients. These results failed to reach statistical significance (\( p = 0.43 \)); however, they showed a positive therapeutic trend in the group of actively treated patients (Figure 5).

**Tolerability**

The combination of octatropine plus diazepam was well tolerated. In total, 60 patients (34.9%) experienced an adverse event. 26 in the octatropine plus diazepam group (15.1%) and 34 in the placebo group (19.8%). Of these, only 12 and 18 adverse events in the respective groups were
considered by the physician to be drug related. The most common adverse events reported during the treatment period were mild-to-moderate abdominal pain, asthenia, cephalgia, abdominal swelling, nausea, and vomiting. The only severe adverse events were one case of abdominal swelling, nausea and epigastralgia reported by a

![Figure 2. Therapeutic success among patients with an abdominal pain/discomfort score of ≥3 at baseline treated for 6 weeks with octatropine plus diazepam or placebo (p =0.059 for octatropine plus diazepam vs. placebo).](image)

<table>
<thead>
<tr>
<th></th>
<th>Octatropine/diazepam (n = 92)</th>
<th>Placebo (n = 94)</th>
<th>All patients (n = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>29/63 (31.5/68.5)</td>
<td>45/49 (47.9/52.1)</td>
<td>74/112 (39.8/60.2)</td>
</tr>
<tr>
<td>Age (mean ± SD, years)</td>
<td>39.9 ± 11.5</td>
<td>41.8 ± 11.5</td>
<td>40.8 ± 11.5</td>
</tr>
<tr>
<td>Height (mean ± SD, cm)</td>
<td>166.4 ± 7.9</td>
<td>169.1 ± 8.9</td>
<td>167.8 ± 8.5</td>
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<tr>
<td>Weight (mean ± SD, kg)</td>
<td>63.5 ± 11.4</td>
<td>68.2 ± 13.8</td>
<td>65.9 ± 12.8</td>
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<tr>
<td>BMI (mean ± SD, kg/m²)</td>
<td>22.87 ± 3.06</td>
<td>23.77 ± 3.49</td>
<td>23.32 ± 3.30</td>
</tr>
<tr>
<td>No alcohol use, n (%)</td>
<td>51 (55.3)</td>
<td>46 (48.9)</td>
<td>97 (52.5)</td>
</tr>
<tr>
<td>No smokers, n (%)</td>
<td>70 (76.1)</td>
<td>77 (81.9)</td>
<td>147 (79.0)</td>
</tr>
<tr>
<td>Dietary restrictions (n)</td>
<td></td>
<td></td>
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<tr>
<td>Low salt</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low calorie</td>
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<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Low fat</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pain/discomfort during run-in period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (mean ± SD)</td>
<td>1.68 ± 0.93</td>
<td>1.62 ± 1.14</td>
<td>1.65 ± 1.04</td>
</tr>
<tr>
<td>Days (mean ± SD)</td>
<td>10.86 ± 3.94</td>
<td>10.31 ± 4.20</td>
<td>10.58 ± 4.07</td>
</tr>
<tr>
<td>Abdominal swelling during run-in period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity (mean ± SD)</td>
<td>1.91 ± 1.03</td>
<td>1.75 ± 1.18</td>
<td>1.83 ± 1.11</td>
</tr>
<tr>
<td>Days (mean ± SD)</td>
<td>10.90 ± 4.0</td>
<td>10.46 ± 4.30</td>
<td>10.68 ± 4.14</td>
</tr>
<tr>
<td>Bowel movements/day (mean ± SD)</td>
<td>1.26 ± 0.87</td>
<td>1.30 ± 0.95</td>
<td>1.28 ± 0.91</td>
</tr>
<tr>
<td>Patients with active disease (pain and discomfort score ≥3 at inclusion visit), n (%)</td>
<td>10 (10.9)</td>
<td>14 (14.9)</td>
<td>24 (12.9)</td>
</tr>
</tbody>
</table>

SD = standard deviation.

![Figure 3. Effect of 6 weeks’ treatment with octatropine plus diazepam or placebo on abdominal swelling scores in patients with irritable bowel syndrome. p <0.05 for week 3 vs. baseline; p <0.001 for week 6 vs baseline in the octatropine plus diazepam group.](image)
Discussion

IBS is a chronic condition which can be improved but not completely resolved by drug therapy. Few studies have provided convincing evidence for the efficacy of drug treatment for IBS. This can be attributed to the lack of objective markers of improvement in IBS and the large placebo response, which is often associated with subjective diseases such as IBS and confounds interpretation of potential clinical benefit.

The present study was designed to evaluate the clinical efficacy of the combination of octatropine plus diazepam (Valpinax®) for the symptomatic treatment of IBS. Patients were selected according to Rome II criteria, having experienced abdominal discomfort/pain for at least 12 weeks (not necessarily consecutive) during the 12 months before entering the study. Patients had also to meet inclusion and exclusion criteria suggested by EMEA guidelines available at the time of the study18. Treatment with octatropine plus diazepam significantly reduced abdominal swelling, pain and discomfort, and the number of bowel movements relative to baseline, but this difference was not significant compared with placebo.

A pre-specified subgroup analysis was conducted in patients with abdominal pain and discomfort of moderate, severe, or very severe intensity at baseline. This symptom is considered as a key feature of IBS, according to EMEA guidelines18, and we may speculate that these patients are in an active phase of disease. Interestingly, only a very low number of patients met this criterion. In this small population, some subjects receiving octatropine plus diazepam achieved therapeutic success compared with no patients receiving placebo, and the between-group difference approached significance. Between-group statistical significance may not have been reached because of the low number of patients included in this sub-analysis. This observation is also supported by the trend towards a reduction in the severity of pain and discomfort in octatropine plus diazepam patients compared with placebo recipients (between-group difference 11%).

The beneficial role of muscle relaxants in IBS has been demonstrated in a meta-analysis, which suggested that these agents are beneficial in IBS patients with abdominal pain as a predominant symptom14. In another meta-analysis of 23 randomized, controlled trials of other muscle relaxants including cimetropium bromide, hyoscine
butyl bromide, mebeverine, otilium bromide, pinaverium bromide and trimebutine, these agents were associated with a global improvement in 56% of patients compared with 38% of placebo recipients ($p < 0.001$)\(^9\).

Our study did not exclude IBS patients free of any symptom of abdominal discomfort/pain at the time of study enrollment. As such, we may hypothesize that some patients may have entered the randomized treatment period in a quiescent phase. Moreover, in most IBS patients, symptoms are intermittent, with severe symptomatic episodes followed by symptom-free days. These results suggest that IBS patients who take part in clinical trials should only be recruited when they are in an active phase of the disease, and always according to Rome II criteria or the more recent Rome III criteria\(^20\).

Although the study design followed the EMEA guidelines for IBS trials\(^18\) and consequently considered the Rome II diagnostic criteria as the basis for subject enrollment, it did not take into consideration the activity level of the syndrome on admission to the study. The inclusion of patients without symptoms may be a flaw in the study design and prevent demonstration of a favourable drug effect. It is evident that it is difficult to demonstrate the improvement of pain/discomfort in subjects that present with only minor or no symptoms at baseline. Rome II criteria may be impractical when considering patients for screening in a clinical trial as there is the high risk of including patients with a "silent" disease status. On the other hand, to include only subjects with a high level of discomfort/pain on admission would increase the sample size beyond reasonable limits for any phase III to IV study. In this study, symptomatic patients accounted for approximately 10% of the enrolled population; therefore, in order to obtain a subset of 200 subjects with a pain/discomfort score of $\geq 3$ in the present study, 2000 Rome II subjects would have needed to be enrolled.

Another limitation of this study is the “subjective” evaluation of efficacy endpoints. However, the study was conducted in accordance with EMEA guidelines current at the time\(^18\). These guidelines state that no widely accepted and validated clinical outcomes are available for the evaluation of IBS patients. A patient’s global assessment of efficacy endpoints is therefore considered as an effective surrogate of validated clinical parameters. Moreover, this subjective evaluation takes into account the effects of the therapy on the quality of life, including depression and anxiety. Another possible limitation could be the use of a placebo control in the presence of other therapies. However, the European guidelines consider the use of placebo as the most appropriate control, since pharmacological therapies are symptomatic\(^18\).

In conclusion, this study suggests the therapeutic efficacy of octatropine plus diazepam for reducing the predominant symptoms of IBS, especially in patients with abdominal pain and discomfort of at least moderate intensity. However, further trials are needed to provide more information on the therapeutic activity of octatropine plus diazepam. Future experimental design should consider only patients in the active phase of the disease to more accurately determine efficacy.

**References**


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