Interactions between Symptoms and Motor and Visceral Sensory Responses of Irritable Bowel Syndrome Patients to Spasmolytics (Antispasmodics)

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Abstract

Aim: to evaluate and correlate the symptomatic, motor and sensory responses to two widely used categories of spasmolytic agents in irritable bowel syndrome (IBS).

Methods: 118 patients with IBS, diagnosed by Rome II criteria and 45 healthy individuals were studied. In the IBS subjects, pain severity, as well as the sensory response to rectal balloon distention and rectal and sigmoid motility, were studied at baseline and after two weeks therapy with either oral buscopan (20 mg three times a day, n=37), a buscopan suppository (30 mg once daily, n=21), oral drotaverine (80 mg three times a day, n=30), calcium gluconate tablets (one three times a day, n=16) as a control for oral agents, or calendula suppository (once daily, n=14) as a control for those who received a suppository. Results: Buscopan, whether administered as a tablet or a suppository, produced a significant reduction in pain scores among IBS patients with predominant diarrhea. No significant differences were evident among other IBS subgroups or in response to drotaverine. None of the interventions had any effect on any of the parameters of rectal or sigmoid motility studied. However, both buscopan and drotaverine led to a significant augmentation of the rectal threshold for discomfort/pain among IBS subjects with predominant diarrhea [21.78±2.8 vs 39.60±2.4 (p<0.05), 20.5±2.8 vs 36.84±3.8 (p<0.05) and 22.18±2.8 vs 36.9±2.42 (p<0.05) for oral buscopan, rectal buscopan and oral drotaverine, respectively]. Conclusion: We conclude that the clinical benefits of supposed spasmolytic (anti-spasmodic) agents may relate more to effects on visceral sensation than motility.

Key words


Introduction

Irritable bowel syndrome (IBS) is one of the most important clinical problems in modern gastroenterology. The precise etiology of IBS is not known. Both psychological and emotional factors and chronic stress have been regarded as important initiators of IBS [1]. While, more recently, enteric infection, food intolerance, immune activation and disturbances in the colonic and small intestinal microflora have been proposed as playing a role in the pathophysiology of IBS [2-4], disordered intestinal motility and visceral hypersensitivity have long been regarded of primary importance [5-7]. However, the precise nature of the relationship between any one of these factors and the clinical presentation and/or natural history of IBS has yet to be elucidated [7, 8].

The diagnosis of IBS currently rests, therefore, on symptoms alone or, more precisely, on an aggregation of clinical symptoms. For example, in one of the most commonly used clinical definitions, the Rome II and III criteria [9, 10], IBS is defined by the presence of abdominal pain or discomfort for not less than 12 weeks during the last 3-12 months, which is related to, or improved by, defecation and which may be accompanied by changes in the frequency and/or consistency of the stool.

In Rome II, pain is central to the definition of IBS; considerable effort has been expended, therefore, on attempting to understand the genesis of pain in IBS. Visceral hypersensitivity (VHS) which refers to an increased sensitivity to peripheral stimuli (mechanical, thermal, chemical and other) and which is manifested through the development of pain, motor and/or secretory disturbances in response to a sub-threshold stimulus [6,11-13] is widely regarded as playing a key role. Visceral hyperalgesia (the phenomenon whereby usually non-painful stimuli are appreciated as being painful) is one manifestation of VHS. At present, VHS is considered as the primary mechanism originating and influencing the intensity of the pain syndrome and motility disorder in IBS [6].
The pathogenesis of VHS in IBS is not completely understood. Neurmodulatory peptides, such as serotonin, are now thought to play a most important role [14]. As intraluminal pressure in the large intestine rises, the enterochromaffin cells which line the epithelium produce and release serotonin, which by activating 5-HT₁ receptors, located on afferent (sensory) neurons, results in the generation of ascending sensory impulses from the periphery [15]. In the cerebral cortex, these sensory impulses induce different sensations, including pain. Meanwhile, the activation of 5-HT₃ and 5-HT₄ receptors located on neurons in the submucosal nerve plexus, intensifies peristalsis and promotes intestinal secretion [14, 16].

Other factors may also play a role in the pathogenesis of VHS, including an imbalance in the system which controls ascending pain impulses at the level of spinal interneurons, and a reduction in descending anti-nociceptive input from the cerebral cortex [15, 17].

This focus on VHS has led to a search for agents that could decrease VHS and thus pain. Currently, the agents most widely used in an attempt to reduce pain in IBS are antispasmodics, also termed spasmyltics, directed at intestinal smooth muscle. In the past, it was assumed that these agents acted through an inhibition of muscle “spasm”; their effects on what is thought to be a fundamental abnormality in IBS, VHS, has not, as yet, been studied.

The aim of this study was to examine, in a dynamic fashion, relationships between pain, motility and visceral sensation, among IBS patients being treated with myogenic spasmyltics.

Methods

Patient characteristics
The study was carried out on 118 consecutive patients with IBS, diagnosed in accordance with Rome II criteria [9]. The age of the patients was 33.8±10.4 years; 85 (67.4%) were females. In terms of IBS predominant symptom, 43 had constipation, 25 diarrhea, and in 50 patients pain and bloating dominated the clinical picture. None had consumed antispasmodics prior to study.

The control group comprised 45 healthy individuals free of gastrointestinal symptoms. The age of the control subjects was 32.6± 6.2 years; 20 were male and 25 female.

Method
Pain intensity at baseline and following treatment was estimated with the aid of a visual analog scale. Patients were asked to mark their pain intensity along a 20 cm graduated line where 0 corresponded to an absence of pain and 20 to unbearable pain.

Visceral sensation was assessed in both IBS patients and controls by assessing the response to balloon inflation. Following an overnight fast and the administration of a one liter cleansing enema on the previous evening, a latex balloon connected to a catheter syringe was introduced into the rectum and inflated in a step-wise fashion in 10 ml increments at 1 minute intervals.

The subjective symptomatic response of the patient to balloon inflation was assessed throughout. The minimum pressure, at which discomfort or pain was experienced, was defined for each patient as their threshold for sensation. Colonic motility was assessed at baseline in all patients using the multiple balloon manometry technique. Prior to testing, rectal evacuation was achieved with an enema; all medications that could affect colorectal motility had been discontinued for at least two days. A multi-channel probe incorporating five 2 ml balloons arrayed at a distance of 5 cm from each other was then introduced into the colon under sigmoidoscopic guidance. During the examination the patient lay on their left side with their knees drawn up to the chest. Recordings commenced 15 to 20 minutes after the introduction of the probe and were continued for 2 hours.

All data from sensory and motility studies was displayed on a monitor and subsequently analyzed using the Polygraf gastrointestinal motility recording system (Medtronic, USA-Denmark).

Control data for the colonic motility studies was derived from prior studies of the large intestine of healthy volunteers at the State Scientific Centre of Coloproctology (Moscow, Russia) [18].

Study protocol
On completion of the baseline measurements, 96 of the original 118 patients agreed to participate in the rest of the protocol and were consecutively assigned (in a manner that ensured equal distribution of IBS subgroups to each therapeutic group) to one of five groups and received one of the following medications over the next two weeks:
1. Oral buscopan – 60 mg daily (20 mg three times a day) (n=37);
2. Buscopan suppository, 30 mg once daily (n=21);
3. Oral droperidol – 240 mg per day (80 mg three times a day) (n=30);
4. Calcium gluconate tablets (0.5g one three times a day) (n=16), as a control for oral agents;
5. Calendula (Calendula Officinalis L., or marigold, a herbal preparation) suppository once daily (n=14), as a control for those who received a suppository.

Given the differences in formulation and method of administration of the various medications, subjects were not blinded to their therapeutic agent. Those performing the objective measurements (manometry and sensory testing) as well as those recording symptomatic responses were blinded to the patient’s therapy.

All sensory and motility tests were repeated in each of these groups at the end of the treatment period. As at baseline, all studies were performed in the morning on an empty stomach, the last dose of medication having been taken on the evening before.

Data analysis
Motor activity of the large bowel was represented by recognizable patterns of wave forms which could be classified as segmenting, peristaltic and propulsive. Their differentiation was based on amplitude, propagation and...
temporal occurrence as well as the very specific features of the propulsive waves. Segmenting contractions featured low amplitude waves and were non-propagating. Specific features of peristaltic waves included their distal propagation, high amplitude and intermediate duration. Propulsive waves were rare, related, perhaps to the prior cleansing of the rectum but were very distinctive being of high amplitude, long duration (approx 30 sec) and distinctly propagative. These waves correspond to the high amplitude propagating contractions or power contractions described by others.

In evaluating motor activity, the following values were defined:

a. The magnitude of the tone of intestinal wall, calculated using the formula Tone = 1/ A, where A is amplitude of respiration waves, expressed in mmHg;
b. The median amplitude and duration of individual waves of motor activity;
c. Longitudinal relationships between wave forms (i.e. whether segmenting, peristaltic or propulsive);
d. The index of motor activity calculated using the formula:
\[ \text{Index} = \sum \frac{A \times t}{T}, \]
where A = amplitude of wave, t = duration of the wave, T = the duration of the period of recording registering and \( \sum \) = sum of A x t

e. Timing and intensity of the 1st and 2nd phases of the gastro-colic reflex.

Statistics
For comparisons pre- and post-treatment, within a given group Student’s t-test or Wilcoxon and Mann-Whitney U tests were used, for parametric and non-parametric data, respectively. Where multiple comparisons were performed, the Bonferroni correction was used.

Results
All 96 subjects who entered the randomization phase completed the two-week study (Table I); there were no drop-outs relating to adverse events or otherwise and, indeed, no side effects were reported in relation to any of the therapies.

1. Baseline symptoms and response to treatment (Table I)
As expected, the highest pain scores were recorded at baseline by those IBS patients with predominant pain and bloating. On the visual analog scale, the average intensity of pain at baseline was estimated by IBS patients with predominant pain and bloating at 13 (on a scale whose maximum was 20 points), by IBS patients with predominant diarrhea at 10 points and by IBS patients with predominant constipation at 8 points.

Significant reductions in pain score were achieved only among IBS patients with predominant diarrhea and in response to either oral or per suppository buscopan.

2. Rectal sensation
a. Baseline studies
In the control group, the threshold for the development of discomfort/pain was 43.6±3.2 mm Hg which corresponds closely to previous reports [6]. In the IBS patients, the threshold for the development of discomfort/pain was significantly lower at 24.08 mmHg. Differences in discomfort/pain threshold were also evident between the IBS subgroups, being significantly (p<0.05) lower among those with predominant diarrhea in comparison to those with constipation or pain and bloating: 19.66±4.2 mm Hg vs 33.82±4.78 mm Hg vs 28.17±6.7 mm Hg, respectively.

b. Response to treatment
After treatment with oral buscopan (Table II) in the group of IBS patients with predominant pain and bloating, their discomfort/pain sensitivity threshold increased to 34.64±4.8 mmHg (ns) and 32% of patients reached the normal sensitivity threshold (≥40 mmHg). In the group of patients with predominant constipation the discomfort/pain sensitivity threshold increased to 35.4±2.6 mmHg (ns); normal values were not achieved by any patient in this group. The most striking results of this treatment were in the group of IBS patients with predominant diarrhea: in 58%, their pain threshold for the development of discomfort/pain was 43.6±3.2 mm Hg which corresponds closely to previous reports [6]. In the IBS patients, the threshold for the development of discomfort/pain was significantly lower at 24.08 mmHg. Differences in discomfort/pain threshold were also evident between the IBS subgroups, being significantly (p<0.05) lower among those with predominant diarrhea in comparison to those with constipation or pain and bloating: 19.66±4.2 mm Hg vs 33.82±4.78 mm Hg vs 28.17±6.7 mm Hg, respectively.

Table II. Discomfort/pain thresholds in IBS patients in response to oral buscopan.

<table>
<thead>
<tr>
<th>Clinical types of IBS</th>
<th>Discomfort/pain threshold (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>IBS with predominant pain and bloating (n=17)</td>
<td>29.12±5.9</td>
</tr>
<tr>
<td>IBS with predominant constipation (n=13)</td>
<td>32.61±5.08</td>
</tr>
<tr>
<td>IBS with predominant diarrhea (n=7)</td>
<td>21.78±2.8</td>
</tr>
</tbody>
</table>

Table I. Pain scores at baseline in IBS patients and in response to treatment

<table>
<thead>
<tr>
<th>Preparation</th>
<th>IBS with predominant constipation (n=36)</th>
<th>IBS with predominant diarrhea (n=21)</th>
<th>IBS with predominant pain and bloating (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Oral buscopan</td>
<td>8.2±2.1</td>
<td>5.3±2.2</td>
<td>10.3±2.3</td>
</tr>
<tr>
<td>Buscopan suppository</td>
<td>7.8±2.6</td>
<td>5.0±2.6</td>
<td>10.2±2.2</td>
</tr>
<tr>
<td>Oral drotaverine</td>
<td>8.1±3.1</td>
<td>4.2±2.3</td>
<td>9.8±1.8</td>
</tr>
<tr>
<td>Oral calcium gluconate</td>
<td>8.4±2.2</td>
<td>7.5±2.1</td>
<td>9.8±2.6</td>
</tr>
<tr>
<td>Calendula suppository</td>
<td>8.2±3.6</td>
<td>7.1±1.8</td>
<td>10.8±1.6</td>
</tr>
</tbody>
</table>
sensitivity threshold reaching the normal value (p<0.05).

After treatment with drotaverine (Table III) in the group of patients with predominant pain and bloating the discomfort/pain threshold after treatment increased to 34.22±4.1 mmHg (ns). In the group of patients with predominant constipation the discomfort/pain sensitivity threshold did not increase significantly. For IBS patients with predominant diarrhea, the discomfort/pain sensitivity threshold increased to 36.9±2.42 (p<0.05). None of the other changes were statistically significant and normal values of discomfort/pain sensitivity threshold were not reached in any of the groups.

Table III. Discomfort/pain thresholds in IBS patients in response to oral drotaverine

<table>
<thead>
<tr>
<th>Clinical types of IBS</th>
<th>Discomfort/pain threshold (mmHg)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS with prevailing pain and bloating (n=11)</td>
<td>30.06±5.9</td>
<td>34.22±4.1</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>IBS with prevailing constipation (n=12)</td>
<td>31.08±5.08</td>
<td>35.57±2.1</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>IBS with prevailing diarrhea (n=7)</td>
<td>22.18±2.8</td>
<td>36.9±2.42</td>
<td>p&lt;0.05</td>
<td></td>
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</tbody>
</table>

The use of the placebo preparation (calcium gluconate) produced a minor increase in the discomfort/pain threshold in two IBS patients with predominant pain and bloating, and in one patient from the IBS group with predominant diarrhea (Table IV).

Table IV. Discomfort/pain thresholds in IBS patients in response to oral placebo (calcium gluconate)

<table>
<thead>
<tr>
<th>Clinical types of IBS</th>
<th>Discomfort/pain threshold (mmHg)</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS with prevailing pain and bloating (n=11)</td>
<td>31.02±5.1</td>
<td>32.2±3.1</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>IBS with prevailing constipation (n=6)</td>
<td>31.06±4.18</td>
<td>31.58±6.6</td>
<td>p&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>IBS with predominant diarrhea (n=4)</td>
<td>25.48±2.66</td>
<td>30.8±2.33</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Following treatment with buscopan as a suppository (Table V), IBS patients with predominant pain and bloating showed an increase of their discomfort/pain sensitivity threshold to 33.96±1.4 mmHg (ns) and 23% reached normal values (≥40 mmHg). The group with predominant constipation showed only a slight and non-significant increase of their discomfort/pain sensitivity threshold to 34.22±3.64 mmHg. In the group of IBS patients with predominant diarrhea, a significant increase of the discomfort/pain sensitivity threshold was observed, to 36.84±3.8 mmHg. However, a normal discomfort/pain threshold was not reached by any patient among these groups.

No significant changes or even trends in discomfort/pain threshold were identified in any IBS group following treatment with the placebo calendula suppository (Table VI).

3. Colonic motility

In the IBS patients, the balloon kymographic data revealed hypersegmentary hypokinesia in 67%, hypotonic hypokinesia was observed in 24% and antiperistaltic complexes in 9%. We did not identify any differences in motility parameters either between IBS subtypes or before and after treatment with any of the preparations tested (Tables VII, VIII).

Discussion

This placebo-controlled study investigated relationships between symptomatic, motility and visceral sensory effects of two pharmacological agents (buscopan and drotaverine) which have been developed and are used on the basis of their antispasmodic properties. Buscopan hydrochloride has been shown, in a large placebo-controlled study to relieve IBS-type pain and is widely used for this indication world-wide [19] while drotaverine, a papaverine derivative, and related compounds, such as alverine, have been widely used as a spasmytic agent in obstetrics, urology and gastroenterology [20]. The main finding of this study was that while neither agent had any effect on motor parameters in the rectum and sigmoid colon, the agent that had a symptomatic benefit, buscopan, exerted its principal physiological effects not on parameters of motor activity, but on visceral sensation. Indeed, indices of motor function of the large intestine changed very little following treatment; while a few instances of recovery of intraluminal pressure to normal values were observed, these patients remaining symptomatic. Therefore, balloon kymography, the methodology employed in this study, while producing interpretable recordings of colorectal motor activity, did not prove of value in predicting the likely efficacy of a given therapy.
Visceral hypersensitivity testing, in contrast, proved more useful; increases in the threshold for pain coinciding with a decrease in the patients' experience of pain as a symptom.

Furthermore, it is worth noting that the lower the level of the pain threshold at baseline, the more pronounced the effect, which might explain the low effectiveness of the various preparations among IBS patients with predominant constipation. Indeed, the pathogenesis of VHS in different types of IBS may vary to some extent as may the impact of various pharmacological agents.

Values for visceral sensitivity are considerably influenced by the method employed. It appears that not only the material employed in the manufacture of the balloon, but also the technique of inflation can significantly influence the study outcome. Slow constant inflation results in accommodation of the rectum, while stepwise inflation does not and hypersensitivity has been observed far more often in studies employing step-wise inflation methods. Accordingly, the threshold for pain sensitivity with the more traditional method of slow continuous balloon inflation was significantly lower than with the use of the tracked step technique [21, 22]. Indeed, Lembo et al could not differentiate between IBS subjects and controls when using the constant inflation technique [7]. Apart from methodological issues, it is also evident that variations in perception by individual patients, prior conditioning [23] and psychological factors will also influence the outcome of such tests and present considerable challenges in developing the ideal test for VHS as well as in understanding the pathogenesis of pain in IBS [12]. Pending the development of the ideal technique, balloon inflation employing the step-wise technique remains the most accessible method for assessing VHS in clinical practice. However, it is noteworthy that the threshold for discomfort/sensation documented in this study is remarkably similar to that of Bouin et al, who reported, in their large series of IBS and control subjects that a cut off threshold of 40 mmHg was highly sensitive (90.7%) and specific (71.8%) in differentiating IBS patients from healthy controls [6].

We acknowledge the limitations of the study. It was not formally randomized; however, the demographics of the various groups illustrate that each was representative of the overall population and of IBS in the community. Furthermore, the investigators were blinded to the treatments and as results of objective tests from the bulk of the recorded data, this should have minimized the effects of a failure to randomize. It is also possible that drug effects could have unblinded the patients; we feel that this is unlikely as the one drug that had an effect on symptoms, buscopan, is poorly bio-available when taken orally with associated plasma levels being below levels of detection [24].

In conclusion, in this study, while we observed the presence of visceral hypersensitivity in all IBS patients studied, the lowest threshold for pain sensitivity was noted among those with predominant diarrhea. Among the therapeutic agents studied, the most pronounced effect on the pain sensitivity threshold was reached with buscopan when given orally, and had its greatest impact among those with predominant diarrhea. In contrast, none of the therapies had a major effect on any of the parameters of colorectal motility studied. We propose, therefore, that visceral hypersensitivity and not motor dysfunction may be a more appropriate target for assessing the impact of proposed antispasmodics/spasmolytics in IBS.

**Conflicts of interest**

Nothing to declare.

**References**