Effective Antispasmodic Therapies in IBS – Associated Spams

Reviewed by:

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Irritable bowel syndrome (IBS) is one of the most common chronic functional gastrointestinal disorders. It is characterized by recurrent abdominal pain associated with changes in bowel movements, presenting as constipation, diarrhea, or both. Swelling and bloating are also frequent symptoms.[1]

Subtypes of IBS based on predominant symptoms[1]

Constipation-predominant IBS (IBS-C):
Affects 20–30% of patients.

Diarrhea-predominant IBS (IBS-D):
Affects 20–30% of patients.

Mixed IBS (IBS-M)
A combination of constipation and diarrhea, affects up to 45% of patients.

IBS of undetermined type
Refers to cases where bowel patterns are intermediate and cannot be clearly categorized.

A key distinction between IBS and functional constipation is the recurrent abdominal pain that occurs at least once a week and its temporal relationship with defecation.

Rome IV Criteria for IBS Diagnosis[1]

Abdominal pain recurring at least one day per week in the last three months.

Must be accompanied by at least two of the following symptoms:

- Pain associated with defecation.
- Pain is linked to a change in the frequency of bowel movements.
- Pain related to a change in stool consistency.

Symptoms must have started at least six months before diagnosis and persisted for at least three consecutive months.

Pathogenesis of IBS: A Multifactorial Perspective[2]

1. **Infection, Microbiota, and Gut Permeability:** IBS pathogenesis involves factors like prior enteric infections, altered bacterial flora, and increased gut permeability. In IBS-D, higher colonic permeability correlates with stool frequency. Proteases, such as serine-proteases in IBS-D and cysteine-proteases in IBS-C, lead to increased permeability and visceral hypersensitivity.

2. **Brain-Gut Axis and Psychological Factors:** The brain processes GI tract signals, influencing motility, secretion, and immune function. Alterations in the brain-gut axis and

psychological factors, including chronic stress, can trigger symptoms, with specific brain region activity correlating to symptom severity.

3. **Immune Activation and Mast Cells:** IBS-D shows higher immune activation, including increased mast cells and lymphocytes. Mast cells release trypsin and histamine, and their proximity to nerve endings is linked to the severity of abdominal pain.

4. **Serotonin and Enterochromaffin Cells:** Enterochromaffin cells release serotonin, activating 5-HT3 receptors on sensory neurons and 5-HT4 receptors, which regulate motility and relaxation, contributing to IBS symptoms

5. **Visceral Hypersensitivity and Motility Disturbances:** Visceral hypersensitivity in IBS leads to pain from exaggerated colonic contractions. IBS-D and IBS-M patients exhibit higher baseline muscular tone and hyperreactive motility, with stress and meals exacerbating symptoms. Specific small bowel motility patterns are linked to pain and cramping.

6. **Stress and its Impact on Motility:** Stress plays a crucial role in altering motility, with stress-induced changes replicating those seen in IBS patients. Long-duration stress induces persistent motility abnormalities, including increased short-spike bursts and reduced propulsive effects.

7. **Hypersensitivity and Motility Interplay:** While visceral hypersensitivity and motility disturbances are key to IBS, their connection remains unclear. Both mechanisms require independent treatment approaches.

Antispasmodics in IBS Treatment

Antispasmodics, also known as spasmolytics, have been used for decades to treat IBS. They are classified into two groups: directly acting smooth muscle relaxants (e.g., drotaverine, mebeverine, papaverine, peppermint oil) and anticholinergic agents (e.g., dicyclomine, camylofin, hyoscine, butylscopolamine, cimetropium bromide, pirenzepine).[2]

Anticholinergic medications cause central and peripheral adverse effects. Central effects include headache, memory impairment, cognitive decline, agitation, and delirium, especially at high doses. Peripheral effects involve hyperthermia, tachycardia, dry mouth, constipation, urinary retention, blurred vision, and reduced sweating.[3]

Antispasmodics like hyoscyamine, dicyclomine, propantheline, and mebeverine are commonly used but are often limited by anticholinergic side effects. In comparison, drotaverine effectively relaxes intestinal smooth muscle, alleviating pain without the adverse effects associated with anticholinergics.[4]

Anticholinergic/Antispasmodics in IBS Management[2,5]

Various antispasmodics are used to manage IBS, including anticholinergics like dicyclomine, hyoscine, and hyoscyamine, as well as direct smooth muscle relaxants such as drotaverine, mebeverine, alverine citrate, otilonium bromide, pinaverium bromide, and trimebutine. While dicyclomine and hyoscine show efficacy in symptom relief, their anticholinergic side effects may limit their use. Mebeverine effectively reduces colonic hypermotility with minimal adverse effects, while alverine, especially with simethicone, improves pain and bloating. Otilonium bromide, with its prolonged colonic action, is particularly beneficial for IBS-D. Pinaverium reduces gut hypersensitivity and motility issues, though its use in pregnancy is uncertain. Trimebutine, acting on opioid receptors, shows promising results but has weak guideline recommendations due to low-quality evidence.

Drotaverine is a directly acting smooth muscle antispasmodic drug with a relaxant effect on smooth muscles of the GI tract. Importantly, it is devoid of the troublesome anticholinergic adverse effects that many other antispasmodics such as dicyclomine, hyoscyamine, and mebeverine are commonly associated with. Its smooth muscle relaxing effect appears to be mediated by changes in intracellular calcium distribution and inhibitory effect on phosphodiesterase. The efficacy of drotaverine on abdominal pain symptoms in IBS patients has been reported in some studies.[4]

Efficacy and Tolerability of Drotaverine in Patients with Irritable Bowel Syndrome[4]

Objective

To evaluate the efficacy and safety of drotaverine hydrochloride (HCl) 80 mg, administered thrice daily, in providing symptomatic relief for patients with irritable bowel syndrome (IBS).

Methods

- A multicentric, randomized, double-blind, placebo-controlled study was conducted at three centers.
- Patients meeting the Rome II criteria for IBS were randomized into drotaverine and placebo groups (n=180).
- Abdominal pain frequency, severity, and stool frequency were assessed weekly over a 4-week treatment period.
- The Subject Global Assessment of Relief (SGA) of IBS symptoms was evaluated at the study's conclusion.

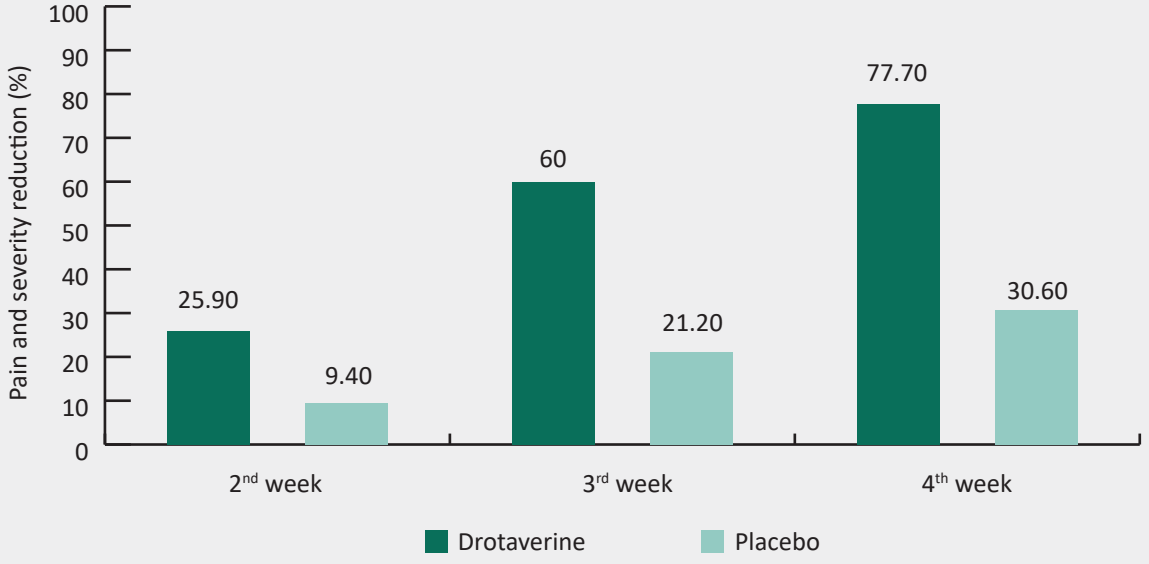
Results

- The drotaverine group showed a significant reduction in pain frequency at the end of week 2 compared to the placebo group ($P < 0.01$).
- Pain severity scores improved significantly in the drotaverine group ($P < 0.01$). Global relief of abdominal pain, as perceived by patients (85.9% vs. 39.5%) and clinicians (82.4% vs. 36.5%), was significantly greater in the drotaverine group ($P < 0.01$).
- Stool frequency also improved significantly with drotaverine compared to placebo ($P < 0.01$). Drotaverine HCl was well tolerated, with no major adverse effects reported.

Conclusion

A 4-week course of drotaverine HCl 80 mg thrice daily significantly improved the abdominal symptoms and stool frequency in IBS patients and is well-tolerated.

Figure 1: Pain and severity reduction in drotaverine vs placebo



Superior Efficacy of Drotaverine Over Mebeverine in Alleviating Pain and Bowel Symptoms in Irritable Bowel Syndrome[6]

Objective

To evaluate and compare the efficacy of Drotaverine and Mebeverine in alleviating pain severity, frequency, and associated bowel symptoms in patients with IBS over a 4-week treatment period.

Methods

- In this 4-week study, 200 patients meeting the ROME III criteria for IBS were randomly assigned to receive either Drotaverine 80 mg (Group A, n = 100) or Mebeverine 135 mg (Group B, n = 100) three times daily, one hour before meals.
- The primary outcome was a ≥30% reduction in pain severity, assessed using the Visual Analog Scale (VAS) and Patient Symptom Scores (PSS).

Results

- In the drotaverine group, PSS reduced from 6.02 to 4.8 on day 3, a 70.4% reduction, with 80% of patients experiencing a reduction to mild pain.

Figure 1: Frequency of pain episodes (per week) in Group A and Group B on Day 0 and Day 28

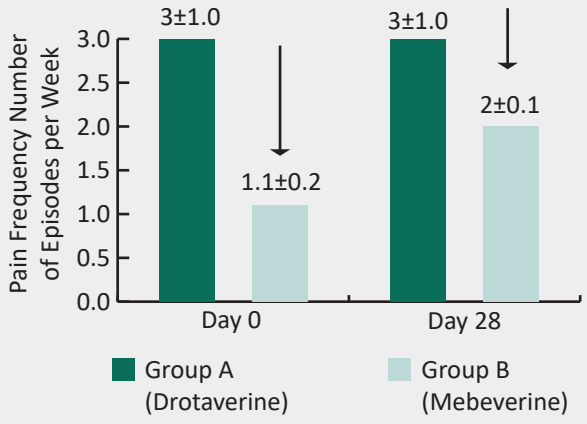
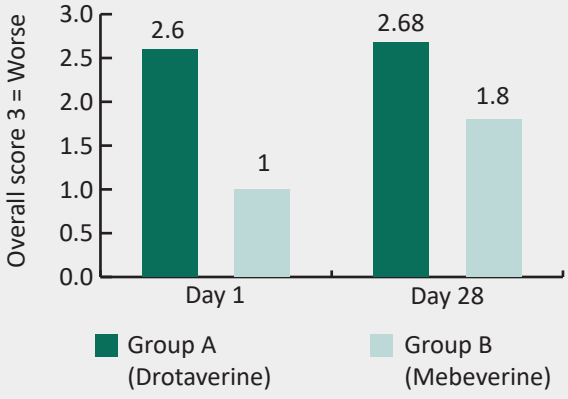


Figure 2: Reduction in Patient's Global Assessment of Symptoms in Group A and Group B



- In contrast, the Mebeverine group showed a smaller reduction from 6.72 to 6.62 (46.1%), and only 40% of patients reported a decrease to mild pain.
- Most patients in both groups initially had moderate to severe pain, but the drotaverine group showed a significantly higher proportion of patients (80%) achieving mild pain compared to the Mebeverine group (40%).
- The decrease in pain frequency from day 0 to 28 was 63.3% in the drotaverine group, compared to 33.3% in the Mebeverine group.
- On day 28, 55% of patients in the drotaverine group achieved a change of 1 Bristol Stool Chart (BSC) form, compared to only 30% in the Mebeverine group.

Conclusion

Drotaverine demonstrated significantly greater efficacy than Mebeverine in reducing IBS-related pain severity (from day 3 onward), pain frequency, and stool-related symptoms, making it a superior option for symptom relief in IBS patients.

Efficacy of Drotaverine in Alleviating Symptoms of Irritable Bowel Syndrome[7]

Objective

To evaluate the efficacy of Drotaverine in alleviating symptoms of IBS, particularly abdominal pain, bloating, stool frequency, and colon transit time, in a double-blind, randomized, placebo-controlled study.

Methods

- **Participants:** 62 IBS patients (53 females, 9 males; mean age 50.8 ± 14.2 years) with constipation.
- **Study Design:** Double-blind, randomized, placebo-controlled study.
- **Intervention:** Patients were assigned to receive either Drotaverine (3 x 2 tablets of 80mg) or placebo for 8 weeks after a 2-week pretreatment period.
- Symptoms were recorded daily, including abdominal pain, stool frequency, bloating, dyspepsia, and colon transit time (measured using radioopaque markers).

Results

- Drotaverine significantly reduced abdominal pain by 47%, while pain severity in the placebo group increased by 3%.
- Bloating showed a mild reduction in the Drotaverine group as compared to placebo.
- Dyspepsia and constipation did not show significant improvement in either group.
- No significant adverse effects were observed during the treatment period.

Conclusion

Drotaverine effectively reduces abdominal pain and bloating in IBS, but the placebo effect was substantial, with 48% of patients in the placebo group reporting benefit.

Conclusion

Conclusion Irritable bowel syndrome (IBS) is one of the common GI disorders seen in both primary care and gastroenterologist practice. Abdominal pain is a cardinal symptom of IBS with a considerable negative effect on the quality-of-life of the affected patients. Drotaverine is an antispasmodic smooth muscle relaxant, with some studies documenting its efficacy in managing troublesome symptoms of abdominal pain and/or discomfort in patients with IBS. It is devoid of anticholinergic adverse effects unlike some of the other antispasmodics. Its efficacy in improving the severity and/or frequency of abdominal pain has been shown in clinical studies evaluating IBS patients. A study showed that drotaverine led to a greater reduction in pain severity and frequency, as well as a higher rate of complete spontaneous bowel movements, compared to mebeverine in IBS patients. Drotaverine is an antispasmodic worth considering for the management of abdominal pain control in IBS.

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