Role of Drotaverine in Irritable Bowel Syndrome

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Introduction

Irritable bowel syndrome (IBS), a common gastrointestinal (GI) disorder, linked to disruptions of gut-brain interaction, is characterized by pain in the abdomen along with change in bowel habits.[1,2]

IBS markedly affects an individual's quality of life.[2] The condition has been reported to be common among Indians. Community-based studies have shown the prevalence to range between 0.4% and 4.2%. Additionally, in our country, it is equally common among both men and women.[3]

Various factors are at play when it comes to the development of IBS. These include central and peripheral factors (Table 1). Genetic factors may contribute to both central and peripheral mechanisms.[4]

Presentation of IBS

Patients with IBS can present with abdominal pain and change in bowel habits with diarrhea, constipation, or both.[1] The patient can also present with bloating, distention, and symptoms occurring following food intake.[1,5]

Table 1. Pathogenesis of IBS

Central	Peripheral
Cognitive dysfunction	Abnormal motility
Psychological stress	Inflammation and altered permeability of the gut
Sleep dysfunction	Dysbiosis of the gut microbiota, small intestinal bacterial overgrowth (SIBO), host and microbe interaction
Altered emotional arousal system response	Bile acid malabsorption
	Diet
	Infections
	Visceral hypersensitivity

IBS can be categorized into the following:[1]

- Diarrhea-predominant IBS (IBS-D)
- Constipation-predominant IBS (IBS-C)
- Mixed-type IBS (IBS-M).

Criteria for IBS

IBS is characterized by recurring pain in the abdomen tied to defecation or an alteration in bowel habits. In the latest Rome IV criteria, it is defined as:[5,6]

Recurring abdominal pain occurring on a minimum of one day per week, on an average, over the past 3 months. This is accompanied by ≥2 of the following—

- Linked to defecation

- Associated with a modification in stool frequency
- Associated with a modification in stool form.

The criteria must be met for the previous 3 months and onset of symptoms should be 6 months or more prior to diagnosis.

However, according to a recent Indian consensus statement, in India, Rome III may be favored for diagnosing IBS on account of greater sensitivity (Grade of recommendation B).[3]

Management of IBS

The aim of IBS treatment is to alleviate symptoms, including pain, cramps, bloating, diarrhea, and constipation.[1]

Education and lifestyle modification

Management begins with educating and reassuring the patients. Lifestyle modifications and dietary changes are advised as part of conservative management. This involves increased exercise and promoting healthy dietary changes like making adjustments in alcohol consumption, caffeine intake, consumption of spices, etc. Clinicians may also think of adjusting fiber intake.[5]

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) may have a beneficial role in IBS.[2]

Pharmacological management

Treatment is guided by the dominant symptom.[5] First-line pharmacological management includes antispasmodics, antidiarrheal agents, and laxatives.[2]

Antispasmodics

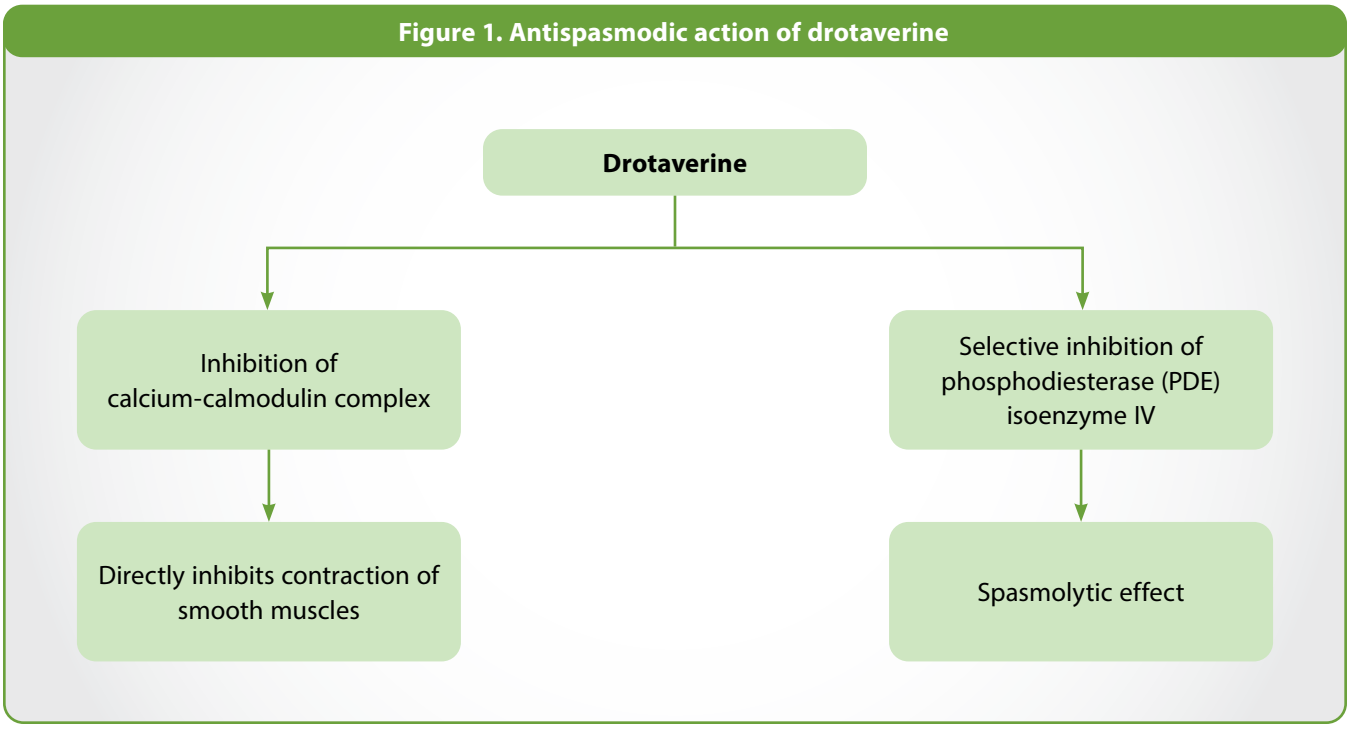
Considering that spasms and dysmotility may cause the symptoms of IBS and antispasmodics play a role in relaxing the smooth muscles in the gut, it is judicious to use these agents to manage pain and bloating.[2] Additionally, abdominal pain has been attributed to smooth muscle spasms. Hence, antispasmodic agents have a role in its management.[7]

However, several antispasmodics, such as mebeverine, hyoscyamine, and dicyclomine, have various anticholinergic adverse effects linked to their use.[7] On the other hand, drotaverine, another antispasmodic agent, relaxes the smooth muscles of the intestine, thus relieving pain, without having the adverse effects seen with anticholinergics.[7] The effect of drotaverine can be explained by its dual antispasmodic action (Figure 1).[8]

Antidiarrheal drugs

Antidiarrheals like loperamide can be used to manage diarrhea in IBS and its use has been suggested in guidelines. However, evidence supporting its efficacy

Figure 1. Antispasmodic action of drotaverine



is limited.[2] Additionally, its use may be associated with adverse effects like nausea, cramps, constipation, and bloating.[5]

Laxatives

Laxatives are used to treat IBS-C. Osmotic as wells as stimulant laxatives seem to be effective in chronic constipation. However, lactulose may be associated with bloating, and must not be used.[2] Polyethylene glycol can be associated with improvement in stool frequency and consistency; however, it may not significantly impact abdominal pain or bloating.[5]

Second-line pharmacological therapy

Second-line agents can be considered if the patients do not respond to first-line pharmacotherapy. For diarrhea, the drugs include rifaximin, eluxadoline, ondansetron, and bile acid sequestrants.[2,5] For constipation, one may consider lubiprostone and linaclotide.[2,5]

Use of tricyclic antidepressants or selective serotonin reuptake inhibitors can also be considered. These neuromodulators may affect the gut-brain pathways and bring about improvement in IBS.[2]

Psychological treatment

Patients with IBS may also benefit from psychological and behavioral therapies. Treatments like cognitive behavioral therapy can help improve the symptoms of IBS.[5] Gut-directed hypnotherapy has also been found to be effective.[2]

Role of drotaverine in pain management in IBS

Numerous studies have shown the efficacy of drotaverine in pain management in IBS.

A randomized, double-blind, placebo-controlled trial included patients with IBS and constipation. Patients received treatment with drotaverine or placebo. Abdominal pain was significantly decreased by 47% in the group receiving active treatment. On the contrary, there was an increase of 3% in pain severity in the placebo arm.[9]

Another study recruited 70 consecutive IBS patients and compared the effects of drotaverine and placebo. Table 2 shows the proportion of patients with a reduction in pain frequency in the two study groups. There was a significant reduction in pain severity scores in the drotaverine arm vs. placebo at 4 weeks (71.4% vs. 31.4%). There were no adverse effects.[10]

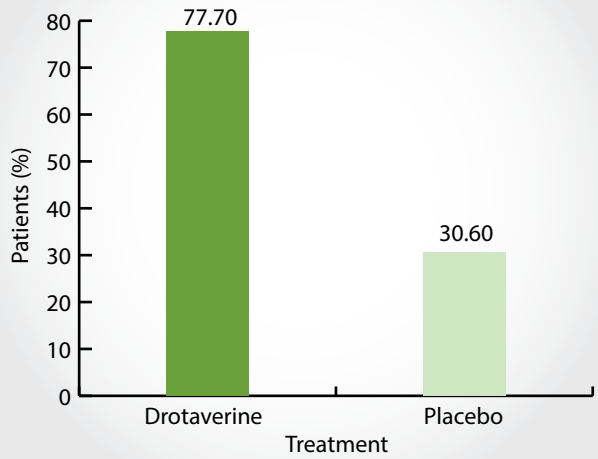
Table 2. Patients with a reduction in pain frequency at the end of 2 and 4 weeks

Group		Patients (%)
Drotaverine	2 weeks	31.4
	4 weeks	71.4
Placebo	2 weeks	5.7
	4 weeks	31.4

Rai and colleagues evaluated the drug's safety and efficacy in IBS patients. At the end of Week 2, 3, and 4, a significant reduction in pain frequency was noted in 25.9%, 60%, and 77.7% patients, respectively, in the drotaverine arm, compared to 9.4%, 21.2%, and 30.6%, respectively, given placebo. Additionally, after Week 4, the drotaverine arm had a significant reduction in pain severity scores in comparison with placebo (Figure 2). The study also reported a statistically significant global relief in abdominal pain in the drotaverine arm, compared to the placebo arm (perceived by both patients and clinicians). Stool frequency also improved significantly in the drotaverine group at the end of Week 3 and 4 compared to placebo group. Drotaverine was safe and was tolerated well by the patients.[7]

Xue and colleagues also conducted a randomized controlled study to determine the efficacy and safety of

Figure 2. Proportion of patients with reduction in pain severity scores



drotaverine in IBS patients. Patients were randomized to treatment and placebo groups. Pain intensity, stool frequency and Bristol score were significantly decreased in the treatment group vs. the placebo arm. There were no serious adverse effects in the two groups. Drotaverine was thus found to have the potential to alleviate symptoms in IBS patients.[11]

A self-controlled study, conducted at multiple centers, evaluated the safety and efficacy of drotaverine in IBS. Patients received treatment with oral drotaverine for 2 weeks. There was a significant reduction in average weekly pain score from 1.42±0.42 to 0.66±0.59, with an overall efficacy rate of 77.9%. A significant increase was noted in average daily stool frequency in IBS-C group from 0.6±0.4 to 0.8±0.3, while a significant reduction was evident in IBS-D group from 2.8±1.2 to 1.6±0.8. There were no serious adverse events during the study.[12]

Drotaverine has been found to be better than another antispasmodic, namely mebeverine, in IBS. A study was conducted to determine the efficacy of drotaverine and mebeverine in IBS patients. One hundred patients each received treatment with drotaverine and mebeverine. There was a 70.4% decline in pain severity at study end in drotaverine group, compared to a 46.1% reduction in mebeverine group (Figure 3). Additionally, there was a significant decrease in frequency of pain (Table 3).[8]

Figure 3. Pain severity score in drotaverine and mebeverine groups

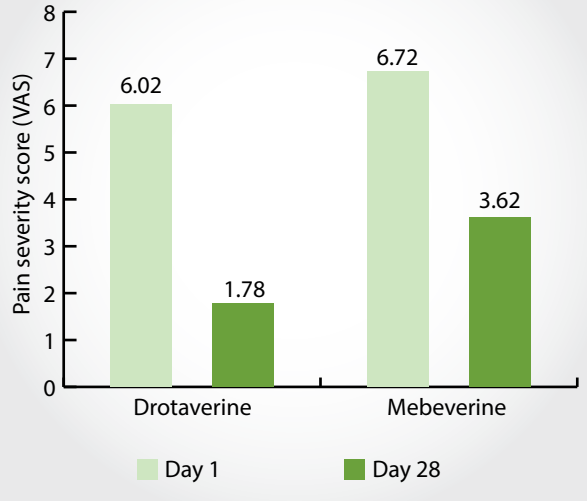


Table 3. Number of pain episodes in a week in drotaverine and mebeverine groups

Groups	Day 0	Day 28
Drotaverine	3±1	1.1±0.2
Mebeverine	3±1	2±0.1

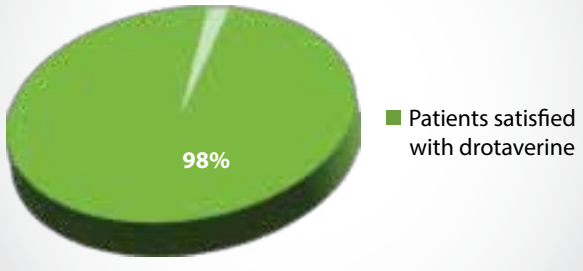
Patients in the drotaverine group also exhibited a significant decrease in straining (45% reduction vs. 15% reduction) vs. mebeverine group. Furthermore, there was a significant difference in attaining complete smooth bowel movement in drotaverine vs. the mebeverine group. Drotaverine was significantly more effective than mebeverine in reducing pain severity, frequency, and stool-related symptoms.[8]

Real-world data on drotaverine in abdominal symptoms

A recent questionnaire-based study enquired patients about the reasons for using drotaverine, its efficacy and satisfaction with its use. General practitioners were asked about drotaverine's status in practice. A total of 650 patients were included in the study. Overall, 74% of the patients took the drug for abdominal pain, 67% took it for cramps, and 19% took it for abdominal discomfort. In terms of onset of action, 15% of the patients considered it to be very fast and 78% considered it as rather fast. A vast majority of the patients were satisfied with the drug (Figure 4).[13]

A total of 210 general practitioners were a part of the study. They found drotaverine to be more favorable in clinical practice for abdominal pain or cramps. In comparison with other antispasmodics, such as

Figure 4. Patients satisfied with drotaverine



hyoscine, mebeverine, and alverine, ketoprofen, and herb formulations, drotaverine appeared to have greater effectiveness and tolerability, and a greater effect on the patient's quality of life.[13]

Conclusion

IBS is a common GI disorder characterized by the troublesome symptoms of abdominal pain, diarrhea, constipation, bloating, and distention. The condition has a considerable impact on a patient's quality of life. The pathophysiology of this disorder is multifactorial with both peripheral and central factors at play.

Aimed at relieving the symptoms of pain, bloating, diarrhea, and constipation, management of IBS includes educating and reassuring the patients, along with introducing lifestyle changes and dietary modifications.

Guided by the dominant symptoms, pharmacotherapy includes the use of antispasmodics, antidiarrheals, and laxatives. With the possibility that dysmotility and spasm may have a role in causing symptoms in IBS, antispasmodics have a potential role in managing IBS as they cause relaxation of the smooth muscles of the gut. However, not all antispasmodics are alike. There are several agents that cause anticholinergic side effects.

Drotaverine, with its direct inhibition of smooth muscle contractions, relieves pain without having anticholinergic adverse effects. It has been shown in various studies to be effective in managing pain in IBS patients. It has favorable effects on pain frequency and pain severity scores while being safe and well-tolerated.

It has been reported to be superior to mebeverine in reducing pain severity, frequency, and stool-related symptoms.

Patients not responding to first-line pharmacotherapy can be considered for second-line therapy. Psychological and behavioral therapies may also benefit patients with IBS.

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