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Review Article

Irritable bowel syndrome and role of pinaverium bromide: pharmacological profile and clinical efficacy

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ABSTRACT

Irritable bowel syndrome (IBS) is a common gut brain interaction disorder that is diagnosed via patient-reported symptoms and various diagnostic criteria. Multiple factors, such as visceral hypersensitivity, gut dysbiosis, dysmotility, gut-brain dysregulation, lifestyle, and dietary habits, are involved in the development of IBS and manifestation of its symptoms of abdominal pain, bloating, and abnormal bowel movements. Lifestyle modifications and dietary changes, behavioral therapy, and pharmacological treatments, namely antispasmodics and antianxiety drugs, are commonly prescribed for IBS management. Pinaverium bromide is a selective calcium channel blocker that acts locally in the gastrointestinal tract and relieves spasms making it an effective agent for the treatment of IBS. This review provides a background on the diagnostic criteria and pathogenic mechanisms of IBS from an Indian clinician standpoint and provides an in-depth overview on clinical studies of pinaverium emphasizing its role in IBS treatment.

Keywords: Calcium channel blocker, Gut-brain disorder, Irritable bowel syndrome, Pinaverium, Post-treatment therapeutic effect

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder characterized by recurrent abdominal pain associated with defecation or a change in bowel habits, which include constipation, diarrhea or a mix of constipation and diarrhea.[1] Based on the predominant stool pattern, IBS is classified into four subtypes, namely, IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed bowel habit (IBS-M), and IBS with unclassified stool pattern (IBS-U). IBS falls under the class of functional gastrointestinal disorders (FGIDs) or gut-brain disorders that include chronic and recurrent symptoms not explained by structural or biochemical abnormalities accounting for almost 40% of referrals to gastroenterology clinics.[2] Motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system processing are all implicated in the pathogenesis of FGIDs. FGIDs are diagnosed via patient-reported symptoms and diagnostic criteria such as Rome, Manning, and the Asian consensus criteria. Lack of a specific biomarker or objective test for these conditions, makes overlap between different FGIDs such as functional dyspepsia (FD) and IBS common and challenging.[3] Functional dyspepsia (FD) is an upper gastrointestinal tract motility disorder with symptoms such as epigastric pain and postprandial fullness. Overall, IBS and IBS-FD overlap cause psychosocial distress to patients, negatively impact quality-of-life (QoL), and result in considerable healthcare and societal costs. A recent meta-analysis showed a significant decrease in health related QoL across all domains when patients with IBS were compared to healthy controls who showed improvement following psychological interventions.

IBS is associated with high healthcare costs driven by increased consultations, mental healthcare visits, and

indirect costs associated with absenteeism and productivity losses. Furthermore, unnecessary diagnostic testing adds to patient and provider expenditure. An economic impact study on IBS in the United Kingdom estimated a £1.3-£ 2 billion direct healthcare cost for IBS diagnosis.[4]

Understanding the global prevalence and distribution of IBS, its pathophysiology and risk factors, and appropriate diagnostic criteria are critical in prescribing suitable pharmacological treatments. This review includes information on the epidemiology and pathogenesis of IBS, clinical diagnostic criteria, and current therapies for IBS with a focus on the safety and efficacy of pinaverium bromide from an Indian perspective.

EPIDEMIOLOGY: PREVALENCE AND DISTRIBUTION OF IBS

The prevalence and distribution pattern of IBS varies considerably between Western countries and the East because of differences in sociodemographic factors, dietary habits and lifestyle, genetics, psychosocial comorbidities, and pathophysiology. Furthermore, variations in prevalence estimates between studies from the same geographical region have been observed and are attributed to methodological differences in diagnostic criteria, data collection methods, and study populations.5 For example, a systematic review and meta-analysis showed a wide variation of prevalence in IBS ranging from 3.3% in France to 31.6% in Nigeria ($p<0.0001$). The same study also showed a broad range of results between different studies from the same country due to differences in research methodology.[6] To obtain prevalence rates that are representative of actual differences in disease burden between countries or within the same country, standardization of data collection methods and diagnostic criteria is necessary.

The Rome Foundation conducted an extensive epidemiological study for FGIDs across 33 countries using uniform methodology in terms of diagnostic criteria, with differing data collection methods between countries (internet-based or in-person interviews). The overall prevalence rate of IBS in countries where data were collected via internet surveys was 4.1% and via household surveys was 1.5%. In India where data was obtained from in-person interviews, IBS prevalence was 0.2% according to Rome IV criteria and 0.4% according to the less restrictive Rome III criteria. Overall, the prevalence rates of IBS showed less variability across countries using the Rome IV criteria. Differences in country-wise prevalence were attributed to cultural and social differences, genetics, and diet. Subgroup analyses showed a higher prevalence among females, with IBS-C being the dominant sub-type, whereas the correlation between age and prevalence differed depending upon the data collection method.[5] A more recent meta-analysis including the Rome Foundation study and several others showed a global pooled prevalence of 9.2% when Rome III criteria were used (n=53 studies) and a pooled prevalence of 3.8% when Rome IV criteria were used (n=6 studies). There was significant heterogeneity between the studies that remained after accounting for methodological differences indicating true country-wise prevalence differences.[7]

Community-based epidemiological studies in rural areas in India showed an IBS prevalence of 4.0%-4.2% whereas a study from Mumbai showed a prevalence of 7.7%. The difference in prevalence rates can be attributed to varying diagnostic criteria and study designs. Thus, utilizing uniform research methodologies and diagnostic criteria are of utmost important for obtaining true IBS prevalence

ETIOLOGY AND RISK FACTORS FOR IBS.

The etiology of IBS is poorly understood but multifactorial and can be attributed to hereditary factors, infections and inflammation, psychosocial factors, and food intolerances.[8]

Genetics

Significant familial association of IBS amongst relatives and a higher concordance of IBS between monozygotic twins (33.3%) versus dizygotic twins (13.3%) is suggestive of a genetic component.[9] Genetic mutation of the SCN5A gene that encodes the voltage-gated sodium channel in the gastrointestinal smooth muscles has been observed in some patients with IBS.[10] Single nucleotide polymorphism in tumor necrosis factor superfamily 15 (TNFSF15) and in genes encoding for TNFα have been associated with IBS-D although there are conflicting results for this association. Additionally, epigenetic changes such as differential DNA methylation in several CpG sites in peripheral blood mononuclear cells between patients with IBS and healthy controls have also been observed. Although several genes have been explored and linked to immune responses, data on genetic involvement is under dispute because of the small sample size of the cohorts studied.

Infections and inflammation

Post-infectious IBS (PI-IBS) is characterized by the occurrence and persistence of IBS symptoms following bacterial gastroenteritis or viral, helminth, and protozoal infections. Alterations in gut wall permeability, inflammation and immune responses and infection-induced changes in gut microflora can lead to IBS. A meta-analysis has shown 6-fold increase in the occurrence of IBS following an infection, with symptom persistence of 2-3 years.[11] Increase in serotonin levels and inflammatory markers have been observed in patients with PI-IBS, indicating involvement of inflammation and immune responses.[12]

Psychosocial factors

The gut-brain axis comprises the central nervous system (CNS), the hypothalamic pituitary axis (HPA), the autonomic nervous system (ANS), and the enteric nervous system (ENS). Bidirectional communication between the gut and CNS and ENS involves neural, endocrine, and neuroimmune pathways that allow the brain to control the motor, sensory, autonomic, and secretory functions of the gastrointestinal tract and also allow the gastrointestinal tract to modulate brain function.13 Early life experiences such as trauma, poor parental relationships, and abuse result in stress and trigger the release of proinflammatory cytokines, which cause cortisol and corticotrophin-releasing hormone (CRF) release, thereby affecting gut homeostasis. Studies have shown a relationship between adulthood abuse and IBS and mood/anxiety disorders although etiological evidence is unclear. Further evidence for support of gut-brain dysregulation triggered by stress in the etiology of IBS is the effectiveness of antidepressants and psychological therapies in the treatment of IBS.

Food and diet

Up to 65% patients report a relationship between their IBS symptoms and consumption of specific foods such as carbohydrate-rich, fatty food, alcohol, coffee, and spicy foods. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) and gluten have been shown to exacerbate symptoms based on their osmotic effects, fermentation, and alteration of epithelial barrier function.[14]

Gender

A meta-analysis of 23 population-based, cross-sectional studies conducted globally showed higher odds for IBS development in females compared to males (odds ratio [OR]: 1.67, 95% confidence interval [CI]: 1.53-1.82).15 Several other studies have also shown a positive association between female gender and IBS development; this association could be linked to the role of sex hormones such as estrogen, differences in health-seeking behaviors, and increased levels of proinflammatory cytokines in women.

Age

Lower odds of IBS in subjects >50 years (OR 0.75, 95% CI: 0.62-0.92) have been observed and can be attributed to decreasing pain perception and symptom recording with advancing age.[15]

Socioeconomic status

Although a lower socioeconomic status is expected to be associated with a lower quality of life and health outcomes, studies have shown conflicting results. A higher socioeconomic status is linked to greater health seeking behavior and diagnosis as seen in some studies. However, a meta-analysis showed a non-significant effect of socioeconomic status on IBS prevalence (n=4 studies).[16]

Smoking

The link between smoking status and IBS development remains inconclusive, with studies reporting conflicting results.

PATHOGENESIS OF IBS

The constellation of symptoms observed in patients with IBS implies a complex pathogenesis leading to the development and aggravation of symptoms. Understanding pathogenesis is important to develop targeted treatments.

Visceral hypersensitivity

This refers to altered sensation in response to physiological stimuli. In patients with IBS, rectal balloon distension studies have shown reduced thresholds of discomfort. Epidemiological studies have shown a VH prevalence of 33%-90% in patients with IBS and especially higher prevalence in IBS-D subtypes.[17] Enhanced pain is perceived in the rectum, colon, parts of the intestine, and esophagus. The exact causes and mechanism of VH are not known, but it is postulated that abnormal processing of sensory information at the level of the peripheral nervous system and CNS are involved. Peripheral mechanisms include immune activation caused by inflammatory or infectious conditions leading to infiltration of T-cells and mast cells and increased sensitivity.[18] mRNA levels of proinflammatory cytokines (interleukin [IL]-6, IL-1β, and tumor necrosis factor alpha [TNF-α]) are elevated in patients with IBS versus healthy controls, thereby indicating the role of inflammation and infection in the sensitization of afferent neuronal fibers in the gastrointestinal tract. Increased release of mast cell mediators, histamine and tryptase in IBS patients and their action on sensory innervations in the gut can lead to increased abdominal pain. Neuroplastic changes in the ENS and afferent pathways via increased density of transient receptor potential vanilloid type-1 (TRPV-1) receptor in the intestinal mucosa can contribute to VH, suggesting TRPV-1 antagonists as potential targets for IBS. Excess serotonin can trigger neuronal afferents leading to hyperalgesia and has been observed in patients with IBS and ulcerative colitis.[19] The involvement of central processes associated with VH is evident from the higher rates of anxiety and depression observed in IBS patients. Compared to patients with ulcerative colitis, patients with IBS show differences in brain responses, such as greater activation of amygdala and other regions, thus indicating decreased activation of pain inhibition areas and increased visceral sensation. Thus, several mechanisms are implicated in VH where it is the underlying cause of abdominal pain.

Understanding these mechanisms will aid in the development of targeted treatments.

Motility disturbances

Altered gastrointestinal motility is postulated to be an important factor in the pathogenesis of IBS although its exact correlation with symptoms is not straightforward. Deceased serotonin levels have been observed in IBS-C patients and increased levels in IBS-D patients.[20] Therefore, serotonin agonists and antagonists have been explored in clinical practice to enhance or slow down gastrointestinal transit. A colonic transit time (CTT) study conducted in IBS patients showed abnormal CTTs to be correlated with abnormal bowel habits.

Dysbiosis of gut microbiota

Imbalances in intestinal microbiome composition and metabolic activities can stimulate immune responses leading to chronic inflammation, VH, increased gut permeability, fatigue, and depression. A meta-analysis showed dysbiosis and altered diversity in IBS patients with deficiency of Lactobacillus and Bifidobacterium and an overgrowth of Enterobacteriaceae and E. coli, suggesting the beneficial role of probiotics.21 Altered fermentation and abnormal pH levels caused by dysbiosis have been observed in colons of IBS patients.

Dysregulation of gut-brain axis

Dysregulation of the gut-brain axis alters the nervous system's reflexive and perceptual responses and results in IBS. The prevalence of anxiety and depression amongst IBS patients implies that it is a gut-brain disorder; however, it is not certain whether the diagnoses of anxiety and depression are made post-IBS diagnoses. Studies have shown that corticotrophin-releasing hormone (CRF), a neuropeptide which modulates the body's response to stress acts centrally and peripherally and stimulates IBS symptoms by changing smooth muscle contractility, mucosal permeability, and visceral sensitivity.[22] Recently, IBS has been suggested to be a disorder of the microbiome-gut-brain axis based on numerous studies that have shown differences in gut microbiota of IBS patients and healthy controls, with evidence of small intestinal bacterial overgrowth (SIBO) in the presence of IBS.[23] Microbiota can interact with the gut-brain axis via modulation of the intestinal barrier and enteric sensory afferents, alteration of bacterial metabolites, and immune regulation, which leads to alterations in motility and immune functions.

DIAGNOSIS OF IBS

The diagnosis of IBS is complicated due to lack of confirmatory laboratory or imaging tests and biomarkers, fluctuations in symptoms, and differences amongst clinicians on the use of diagnostic criteria leading to unnecessary and expensive investigations. From a patient's perspective, the absence of a definitive diagnosis is frustrating, leading to lack of appropriate management. Medical history, routine blood and stool examinations are done to rule out celiac disease and inflammatory bowel disease (IBD) making IBS diagnosis a diagnosis of exclusion. A summary of the diagnostic criteria for IBS has been provided in Table 1.

Table 1: Diagnostic criteria for IBS

Criteria	Signs, symptoms, and investigations to confirm IBS diagnosis
Manning[24]	Abdominal pain with ≥2 of the following: Looser stools and more frequent bowel movements at onset of pain Pain relieved by defecation Abdominal distension or bloating Sensation of incomplete evacuation Mucus in stool
Kruis[25]	Presence of all the following for >2 years: Abdominal pain Flatulence Irregular bowel movements Absence of abnormal physical tests and laboratory investigations (CBC, ESR> 10 mm/h), blood in stool
Rome I[26]	Presence of abdominal pain associated with defecation with ≥2 of the following symptoms for > 3 months: Altered stool frequency Altered stool form Abdominal distension Mucus passage
Rome II[26]	Presence of abdominal pain or discomfort associated with defecation with ≥2 of the following symptoms for >3 months:

Continued.

Criteria	Signs, symptoms, and investigations to confirm IBS diagnosis
	Altered stool frequency Altered stool form Abdominal distension Mucus passage
Rome III[26]	Recurrent abdominal pain or discomfort for ≥3 days per month in the last 3 months associated with ≥2 of the following: Pain/discomfort improved after defecation Onset associated with a change in frequency of stool Onset associated with a change in form (appearance) of stool, alternating between constipation and diarrhea Absence of anatomical changes or 'alarm' symptoms
Rome IV[26]	Recurrent abdominal pain on an average on at least 1 day/week in the last 3 months, associated with ≥2 of the following, with symptom onset at least 6 months before diagnosis: Related to defecation Associated with a change in frequency of stool Associated with a change in form (appearance) of stool
Asian consensus[27, 28]	Recurrent abdominal pain, bloating, or other discomfort for ≥3 months associated with at least one of the following: Relief with defecation Change in stool form with BSFS Change in stool frequency
Indian consensus[29]	Recurrent abdominal pain, bloating, or other discomfort for ≥3 months associated with at least 1 of the following: Relief with defecation Change in stool form with BSFS: type 1-3 as constipation and type 5-7 as diarrhea Change in stool frequency

BSFS, Bristol stool form scale; CBC, complete blood count; ESR, erythrocyte sedimentation rate

Comparison of diagnostic criteria

Although the criteria have evolved and been refined over the years, the symptoms of abdominal pain and discomfort relieved by defecation have remained common from Manning to Rome IV criteria. Frequency of symptoms of ≥3 days per month for 3 months was also included as a diagnostic criterion in most of the recent criteria, excluding Manning criteria, indicating the chronic nature of IBS. A meta-analysis on the global prevalence of IBS using different diagnostic criteria showed pooled prevalence rates of 9.2% and 3.8% with Rome III and Rome IV criteria, respectively.[7] Similarly, a lower prevalence upon application of Rome IV criteria was also seen in a global survey conducted by the Rome Foundation.[11] These data suggest that the Rome IV criteria are more restrictive than Rome III, which may be useful for recruiting homogeneous groups of patients for clinical trials but may undermine true prevalence estimates. In addition, inability to meet the Rome IV criteria can leave a patient undiagnosed leading to increased testing and consultation costs. Therefore, use of Rome III criteria may serve as a broader entry portal for patients with abdominal symptoms. In accordance with global prevalence studies, the Indian consensus statement also stated a preference for Rome III criteria over Rome IV due to its higher sensitivity (9.5% vs. 6.2%) and lower overlap of IBS with functional diarrhea and functional constipation.[30] The Multicentric Indian IBS (MIIBS) study was conducted across 17 centers in India to compare Manning, Rome I, II, III, and Asian criteria for diagnosing and subtyping of patients with chronic lower gastrointestinal tract symptoms and no alarm features. In addition to questionnaire-based assessment of diagnostic criteria, patients were asked to provide self-perception of bowel pattern and predominant stool form using the Bristol stool form scale and subsequently classified into IBS-C or IBS-D subtypes. Of the 1618 patients who participated in the study, 91.2% fulfilled Manning criteria, 67.9% fulfilled Rome I criteria, 40.1% fulfilled Rome II criteria, 52.5% fulfilled Rome III criteria, and 74.5% fulfilled Asian criteria, indicating that Manning and Asian statement criteria were more sensitive toward diagnosing Indian patients with IBS. These results highlight the importance of including patient perception of symptoms in addition to appropriate investigations.[31]

MANAGEMENT OF IBS

Symptom-based management of IBS should be coupled with an approach that targets the underlying pathophysiologic mechanisms. Table 2 contains information on currently used pharmacological treatments for IBS based on pathophysiology.

Table 2: Commonly used pharmacological treatments for IBS based on pathophysiological mechanisms.

Pathophysiology	Drug class	Mechanism of action	Clinical effects	Example	Predominant IBS sub-type
Visceral hypersensitivity and intestinal motility impairment	Antispasmodics	Inhibit binding of acetylcholine to muscarinic receptors and block calcium channels (52)	Improvement in abdominal pain and stool consistency	Otilinium bromide	IBS-C
		Block voltage-operated sodium channels and intracellular calcium accumulation	Improvement of overall IBS symptoms, stool consistency, and general well-being	Mebeverine	IBS-D
		Block calcium channel blockade of gastrointestinal smooth muscles	Improvement in abdominal pain and stool consistency	Pinaverium bromide, alverine citrate	IBS-C
	Opioid agonists/ antagonists	μ-opioid receptor, κ-opioid receptor and δ-opioid receptor agonism to decrease gastrointestinal transit and secretions (53)	Decrease in stool frequency and abdominal pain, increase in stool consistency	Eluxadoline	IBS-D
Impaired gastrointestinal motility	Laxatives and motility accelerants	Osmotic effects Guanylate cyclase C receptor agonist Activation of chloride channels and increased fluid secretion in bowel (54)	Decrease in abdominal pain, improvement in stool frequency, reduction in abdominal pain and bloating	Linaclotide, lubiprostone, polyethylene glycol, lactulose	IBS-C
Altered serotonin metabolism	5-HT receptor agonists and antagonists	Antagonism of 5-HT_3 receptors Agonism of 5-HT_4 receptors (54)	Relief from loose stools, decreased frequency and urgency Stimulation of gut motility	Alosetron, ondansetron, ramosetron Prucalopride	IBS-D IBS-C
Dysbiosis	Probiotics, antibiotics	Restore gut lumen microbiota Decrease local microinflammation (54)	Improvement in abdominal pain, flatulence, bloating	Rifaximin, several probiotics	IBS-D
Gut-brain dysregulation	Antianxiety drugs (SSRIs and Tricyclic antidepressants)	Alteration of cholinergic and/or histaminergic transmission in the gastrointestinal tract Modulation of ascending visceral afferents centrally (54)	Improvement in abdominal pain	Desipramine, amitriptyline, paroxetine, sertraline	IBS-D
Subclinical mucosal inflammation	Antihistamines	Histamine H1 antagonists to prevent sensitizing effect of histamine TRPV1 (55)	Improvement in abdominal pain	Ebastine	IBS-C and IBS-D
Genetic mutation	Sodium channel blocker	Correction of *SCN5A* mutation which affects voltage-gated sodium channels	Restoration of colonic motility	Mexiletine	IBS-C

IBS-C, constipation predomination IBS; IBS-D, diarrhea-predominant IBS; IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor; TRPVI, transient receptor potential vanilloid.

Following dietary and lifestyle modifications, antispasmodics and antianxiety drugs are used as first-line treatment for IBS.

Antispasmodics

Antispasmodics act by a variety of mechanisms. This class includes anticholinergics and antimuscarinic agents, which inhibit binding of acetylcholine to muscarinic receptors (e.g. dicyclomine, hyoscine, and hyoscyamine), thereby causing inhibition of sodium influx and consequently calcium influx into sodium channels (e.g. mebeverine and papaverine) and prevention of calcium influx in gastrointestinal smooth muscles (e.g. peppermint oil, alverine, otilonium, pinaverium, and trimebutine).32 The overall effect is relaxation of smooth muscle spasms via inhibition of contractile pathways and alteration of intestinal and colonic transit time leading to improved stool consistency and reduction in centrally and peripherally mediated pain.

Antianxiety drugs

As IBS is associated with psychiatric disturbances, anxiolytics such as tricyclic antidepressants (TCAs: amitriptyline, desipramine, and imipramine) and selective serotonin reuptake inhibitors (SSRIs: fluoxetine, paroxetine, and sertraline) are often prescribed. Thesedrugs act peripherally by blocking histaminergic and cholinergic pathways and centrally via modulation of ascending visceral afferents and central transmission. In a systematic review and meta-analysis on the efficacy of antidepressants versus placebo in patients with IBS-D, better improvement in global symptom relief was observed with TCAs than with SSRIs.

ROLE OF PINAVERIUM BROMIDE IN IBS TREATMENT

Blockade of calcium channels and gut motility

Voltage-dependent calcium channels (VDCCs) are responsible for the influx of calcium ions (Ca2+) that trigger the contractile mechanism in vascular smooth muscle cells, thereby altering gastrointestinal motility. There are two main types of VDCCs. L-type (long lasting) channels require strong depolarization and are found predominantly in cardiac muscle cells, smooth muscle cells, and some neurons. T-type (transient) channels display transient activation properties and are low-voltage (LVA) channels that are mostly found in neurons.[33]VDCCs regulate intracellular processes such as contraction, secretion, and neurotransmission and thus are a target for a class of antispasmodic drugs known as calcium channel blockers. L-type calcium channels are distributed in gastrointestinal smooth muscles, interstitial cells of Cajal, and nerve terminals of enteric neurons in the ENS and regulate processes such as smooth muscle contractions, motility regulation, and release of neurotransmitters such as acetylcholine and substance P, both of which influence gut motility, secretion, and sensory perception. Thus, it is logical that L-type calcium channel blockers would be useful in IBS as they can relax gastrointestinal smooth muscles and reduce the frequency of high-pressure waves of the colon, thereby improving symptoms of abdominal pain and dysmotility.

Pinaverium bromide: L-type calcium channel blocker

Many studies have cited the role of L-type Ca2+ channels in pathogenesis of abdominal pain. The pathogenic stimuli and type of muscle cells determine the modulation of α1 subunits of the L-type Ca2+ channels. Thus, in the pathophysiology of visceral hypersensitivity, calcium-channels act as an integrator of a variety of noxious inputs. Pinaverium bromide is a quaternary ammonium compound that acts as a selective spasmolytic agent and blocks the L-type calcium channel at the α1 subunit on colonic-smooth muscles by acting on the extracellular dihydropyridine site of the calcium channel. It prevents the influx of calcium ions and stabilizes the non-conducting channel state, thereby inhibiting contractile activity. Smooth muscle cells and interstitial cells of Cajal are targets for pinaverium as it affects slow-wave contraction and frequency. Pinaverium affects colonic activity by preventing the action of acetylcholine post-synaptically and inhibiting the contractile effect of digestive hormones, cholecystokinin, gastrin, and substance.[34]

*Ph*armacokinetics

Pharmacokinetic properties of pinaverium bromide such as its low absorption due to polarization at physiological pH and its high molecular weight (591.42) prevent its diffusion across cell membranes leading to localized action in the gastrointestinal tract. As the drug has a negligible absorption (oral bioavailability <1%), it is devoid of systemic side effects. Metabolism studies have shown that it is predominantly eliminated by the hepatobiliary route, indicating that pinaverium remains in the gastrointestinal tract. Relief from spasms and motility disturbances occurs at doses that do not cause cardiotoxicity.[34]

Clinical studies on pinaverium bromide

Table 3 provides details of clinical studies on pinaverium in IBS patients.[35-46] In a recent meta-analysis involving placebo-controlled trials that evaluated pinaverium for IBS treatment (n=8 studies), pinaverium was found to have a beneficial effect on overall IBS symptom relief with a positive standardized mean difference (SMD) of 0.64 (95% CI 0.45-0.82; p<0.0001). A non-significant effect of gender, age, methodological quality score, or sample size was observed using meta-regression analysis, and there was no publication bias. Similarly, secondary endpoints such as abdominal pain, stool change (consistency/frequency), and bloating were also found to significantly improve in the pinaverium group versus

placebo.47 These results are in line with those of a Cochrane meta-analysis that evaluated the effects of various antispasmodics in IBS patients. There was a significant improvement in relief from abdominal pain when all antispasmodics, including pinaverium, were evaluated together against placebo.[48]

Table 3: Characteristics of pinaverium vs. placebo/active comparator studies in IBS patients.

Study and Country	Type of trial	Diagnostic criteria	Patient characteristics	Treatment and duration	Comparator	Outcome	Safety
Levy 1977 (France)[35]	RCT	Clinical	Male and female patients, mean age 50 years	Pinaverium 50 mg (tid) for 15 days	Placebo (tid)	Significant improvement in global symptom response (p<0.01)	NA
Delmont 1981 (France)[36]	RCT	Clinical	Male and female patients, mean age 56 years	Pinaverium 50 mg (tid) for 28 days	Placebo (tid)	Significant improvement in global symptom response (p<0.01) and abdominal pain (p<0.05)	NA
Awad 1995 (Mexico)[37]	RCT	Rome I	Female patients, mean age 31 years	Pinaverium 50 mg (tid) for 21 days	Placebo (tid)	Significant decrease in pain duration (p<0.01)	NA
Wittman 1999 (Hungary)[38]	CT	Clinical	Patients and healthy controls	Pinaverium 50 mg (tid) for 14 days	None	Significant decrease in abdominal pain, bloating, normalization of stool frequency	NA
Dubarry 1977 (France)[39]	RCT	Clinical	Male and female patients, mean age 40 years	Pinaverium 50 mg (tid) for 6 days	Placebo (tid)	Significant abdominal pain resolution (p<0.01)	NA
Virat 1987 (France)[40]	RCT	Clinical	Male and female patients, average age 44 years	Pinaverium 50 mg (tid) for 7 days	Placebo (tid)	Significant improvement in abdominal pain (p<0.05)	NA
Wu 2015 (China)[41]	RCT	NA	NA	Pinaverium 50 mg (tid)+Wuling capsule 0.33 g/capsule(tid) for 6 weeks	Pinaverium 50 mg (tid)	Significant improvement in abdominal pain, stool frequency and properties (p<0.05), and in QoL, anxiety and depression scores in treatment group (p<0.05)	No SAE in either group
Zheng 2015 (China)[42]	RCT	Rome III	Male and female patients, mean age 37 years	Pinaverium 50 mg (tid) for 4 weeks	Placebo (tid)	Significant improvement in pain resolution, stool consistency (p<0.01), and in pain frequency and stool frequency (p<0.01)	Similar rates of TEAE in pinaverium and placebo group such as constipation, headache, abdominal side effects, anxiety, and back pain
Qin 2017 (China)[43]	RCT	NA	NA	Pinaverium 50 mg (tid) for 4 weeks	Acupuncture (3 times/week for 4 weeks)	Significant improvement in IBS-SSS (p<0.05), and abdominal pain, distension, stool abnormality (p<0.01) in acupuncture group	No AEs

Continued.

Study and Country	Type of trial	Diagnostic criteria	Patient characteristics	Treatment and duration	Comparator	Outcome	Safety
Qu 2012 (China)[44]	RCT	Rome III	Male and female patients, age 18-60 years	Pinaverium 50 mg (tid) for 2 weeks	TCOM	Significant improvement in VAS and BSS scores, and patient self-evaluation scores in TCOM group	No SAE in either group
Sun 2011 (China)[45]	RCT	Rome III	Male and female patients, average age 38 years	Pinaverium 50 mg (tid) for 4 weeks	Acupuncture (1 time/week for 4 weeks)	Significant decrease in symptom score and improvement in QoL ($p<0.01$) in acupuncture group	No AEs in either group
Li 2010 (China)[46]	RCT	NA	NA	Pinaverium 50 mg (tid) for 4 weeks	Acupuncture (3 times/week for 4 weeks)	Significant improvement in QoL score ($p<0.01$) and effective rate ($p<0.01$) in acupuncture group	NA

AEs, adverse events; BSS, bowel symptom score; CT, clinical trial; IBS-SSS, irritable bowel syndrome – symptom severity scale; NA, not available; QoL, quality of life; RCT, randomized controlled trial; SAE, serious adverse event; TCOM, traditional Chinese orthopedic manipulation; TEAE, treatment-emergent adverse event; tid, thrice a day; VAS, visual analog scale.

In placebo-controlled trials, pinaverium was found to significantly improve and resolve abdominal pain and bloating, stool frequency and consistency with minimal side effects. In all trials that involved comparison of pinaverium with treatments like acupuncture and traditional Chinese medicines, a significant improvement was observed with pinaverium in the domain of quality of life (QoL), bowel symptom scale (BSS) scores, and effectiveness percentages versus alternative therapies. However, it is important to note that studies involving alternative therapies were conducted in China and could be biased by geographic and cultural factors, thereby limiting extrapolation on a global scale. Although pinaverium can be used for all subtypes of IBS, most of the trials were conducted in IBS-D patients. Safety information from available clinical trials is limited due to limited number of studies and low sample size, making it difficult to assess the safety of pinaverium versus other antispasmodics/alternative therapies. In trials where adverse events were reported, the events were mild and did not require immediate attention or stoppage of treatment.

In a prospective, observational cohort study conducted in China in IBS patients diagnosed according to the Rome III criteria, a significant improvement was observed in IBS-QoL score following 4 and 8 weeks of treatment with pinaverium.[49] In an open-label trial conducted in 61 south Indian patients, abdominal pain decreased in 49% of patients, stool consistency improved in 74%, straining and urgency decreased in 71%, and mucus decreased in 64% of patients treated with pinaverium, while a good tolerability profile and minimal side effects were observed, supporting the use of pinaverium as an antispasmodic for IBS.[50]

Post treatment therapeutic effect of pinaverium

The chronic nature of IBS necessitates treatment that is not only effective during the treatment period, but also one that continues to prevent post-treatment relapse, a phenomenon known as post-treatment therapeutic effect (PTTE). Studies have shown that IBS drugs display PTTE and prevent recurrence with methods such as cognitive behavioral therapy (CBT) and with pharmacotherapies such as antidepressants and alosetron. The duration of PTTE depends upon the type of treatment.[51] Most studies have failed to accurately characterize PTTE due to insufficient duration of observation and inadequate time to resolution. Zheng et al. conducted a placebo-controlled study evaluating the PTTE of pinaverium in IBS-D patients. Pain intensity and frequency, stool consistency and frequency, adverse events, and IBS global symptom scale scores were compared between the two groups with a follow-up of 57 weeks post-treatment. Pinaverium had a rapid onset of action of 3 days with a significant decrease in all endpoints ($p<0.05$). Although there was no significant change in symptoms between the groups following 1 week of treatment, the symptom scale scores continued to decrease in the pinaverium group. The onset of action was slow and therapeutic effects were maintained for 9-17 weeks after treatment discontinuation following which it was considered IBS natural history. Kaplan-Meier survival analysis showed a significant increase in relapse-free probabilities of all endpoints for pinaverium versus placebo. This study was important and the first of its kind to have a suitable length of observation and capture both the PTTE length and IBS natural history course. The lipophilic properties of pinaverium and its affinity for colonic smooth muscles were postulated to be responsible for post-treatment efficacy. In addition to demonstrating PTTE, this study also showed a rapid onset of action of

pinaverium, supporting its use as a first-line rescue medication for IBS and a cost-effective treatment for the management of refractory IBS.

Side effect profile of pinaverium bromide

Most trials with pinaverium have shown a safety profile comparable to placebo, with mild treatment-related effects that required little to no intervention. Side effects are primarily related to abdominal discomfort, nausea, dizziness, and hypertension. The specific binding of pinaverium to L-type calcium channels on colonic smooth muscles and its pharmacokinetic properties that prevent it from being systemically absorbed are responsible for its localized effects in the gastrointestinal tract.34 Pinaverium does not act on calcium channels in the heart, thereby avoiding cardiotoxic effects. Because pinaverium does not affect acetylcholine levels and does not have a significant action on cholinergic receptors at clinical doses, it is devoid of anticholinergic side effects such as dry mouth, blurred vision, constipation, urinary retention, and confusion. Thus, its rapid onset of action, long PTTE, and mild side effect profile make it a suitable candidate for IBS treatment.

CONCLUSION

The chronic nature of IBS and its high global prevalence necessitate accurate diagnosis and appropriate treatment of the condition. The constellation of symptoms in IBS patients are due to its complex pathophysiological mechanism wherein visceral hypersensitivity is a major factor for abdominal pain that is observed in all IBS patients. Although several criteria have been developed for IBS and various subtypes, diagnosis remains a challenge. In India, Rome III criteria have been shown to be the most relevant for diagnosing IBS due to its broader inclusion criteria and higher sensitivity. Dietary and lifestyle modifications and pharmacological treatments, especially antispasmodics have been shown in several trials to be effective in IBS treatments. Pinaverium bromide is a calcium channel blocking spasmolytic agent that has a localized action in the gastrointestinal tract and a suitable safety profile. Rapid onset of action and long PTTE help maintain remission for an extended period of time, making it a suitable choice as a first-line rescue medication for long-term management of IBS and supporting its inclusion in IBS treatment regimens.

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