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The role of antispasmodics in managing irritable bowel syndrome

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Abstract
Although antispasmodics are the cornerstone of treating irritable bowel syndrome, there are a number of antispasmodic medications currently available in Colombia. Since they are frequently used to treat this disease, we consider an evaluation of them to be important.

Keywords
Antispasmodic, irritable bowel syndrome, pinaverium bromide, otilonium bromide, Mebeverin, trimebutine.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most frequent chronic gastrointestinal functional disorders. It is characterized by recurrent abdominal pain associated with changes in the rhythm of bowel movements with either or both constipation and diarrhea. Swelling and bloating are frequent occurrences. (1)

IBS is divided into two subtypes: predominance of constipation (20-30% of patients) and predominance of diarrhea (20-30% of patients). When both constipation and diarrhea are combined, it is called mixed IBS (up to 45% of patients) and IBS of undetermined type when the pattern of bowel movements is intermediate and cannot be classified as diarrhea or constipation. It is noteworthy that abdominal pain occurring more than once a week plus the temporal relationship of pain with defecation are what theoretically differentiates IBS from functional constipation. (2, 3)

According to the Rome IV criteria, IBS is diagnosed by abdominal pain that recurs at least one day a week plus two or more of the following: pain is associated with defecation; pain is related to a change in the frequency of bowel movements; and/or pain is related to a change of stool consistency. The criteria must be met for three consecutive months prior to diagnosis and symptoms must have started a minimum of six months before diagnosis. (3, 4)

There are no known structural or anatomical explanations of the pathophysiology of IBS and its exact cause remains unknown. Nevertheless, several mechanisms have been proposed. Altered gastrointestinal motility may contribute to changes in bowel habits reported by some patients, and a combination of smooth muscle spasms, visceral hypersensitivity and abnormalities of central pain processing may explain abdominal pain, which is an essential part of the complex of symptoms. (5)

It is estimated that IBS affects 11% of the world's population. In Europe, Asia and the United States its prevalence varies from 10% to 20%. The lowest prevalence in South Asia (7%) while the highest is in South America (21%). In Western countries it is twice as frequent in women. (6) IBS has a significant impact on health-related quality of life, results in lower labor productivity, higher absenteeism and increased use of health care with its attendant costs. In 2005, direct medical costs attributed to IBS in the United States were estimated at USD 1.5 to 10 billion per year. (1) IBS can also affect the doctor-patient relationship since

ineffective control of symptoms can decrease the credibility of doctors and encourage the patient to seek additional opinions. (7)

A heterogeneous group of medications called antispasmodic or spasmolytic drugs has been used in IBS therapy for decades. They act as direct smooth muscle relaxants (papaverine, mebeverin, peppermint oil), anticholinergic agents (butylscopolamine, hioscin, cimetropium bromide, pyrenzepine) or calcium channels blockers (alverine citrate, ethyl bromide, pinaverium bromide). Their goal is to reduce symptoms caused by defecation through increasing colonic transit time, improving stool consistency and/or reducing stool frequency. (2) The pharmacological action of these agents is not always clear, and their mechanisms are often mixed. However, metaanalyses of studies comparing antispasmodics with placebos or other treatments have consistently confirmed the positive effects of these drugs, and their side effect profiles have been excellent. (8)

PATHOPHYSIOLOGY

The pathogenesis of IBS is considered to be multifactorial. A history of gastrointestinal infections, colonic or bacterial flora of an altered small intestine, increased intestinal permeability and immune activation may all play roles in the development of the disease. (9) Signals from the gastrointestinal tract are processed in the brain and can influence motility, secretion and immune function. The brain-gut axis is essential for regulation of the gastrointestinal system, so structural or functional alteration can lead to the development of disorders such as IBS. (10) Consequently, psychological factors and chronic stress may also be involved in triggering symptoms. (11)

Abnormal intestinal motility and visceral hypersensitivity remain the main factors in the pathogenesis of the disease. (12) Intraluminal factors such as serine proteases may increase colonic permeability of IBS patients by activating the protease-activated receptor-2. This results in visceral hypersensitivity. (13) Similarly, luminal cysteine proteases have been shown to increase colonic permeability through degradation of binding proteins resulting in visceral hypersensitivity possibly secondary to local microinflammation. (14) Immune activation of the colonic mucosa has been found to be significantly greater in IBS patients than in healthy controls. (15) In addition, mast cells have been implicated in the development of IBS. One study found that the number of mast cells in the colonic mucosa and the amounts of trypsin and histamine they released were markedly higher in IBS patients than in controls. (16) Mast cells in the vicinity of nerve endings has been significantly correlated with the severity and frequency of abdominal pain and discomfort in IBS patients. Enterochromaffin cells also play an important role in the development of visceral hypersensitivity because they produce and release serotonin which activates 5-HT3 receptors located in afferent sensory neurons. (17)

Abnormalities in colonic motility patterns are characterized by hyperreactivity due to prolonged increase of colonic motor activity after meals, increased motor activity in response to stressors or cholecystokinin (CCK), and increased motor response to abdominal distention. (18)

Visceral hypersensitivity alone is not painful, but it can cause abdominal pain in IBS patients due to the effect of any intense stimulus such as an exaggerated contraction of the colon. (19) Nevertheless, it has not been possible to establish a clear relationship between visceral hypersensitivity and motility disorders, and these two factors have generally been considered to be independent, and both require effective treatment. (20)

Voltage Dependent Calcium Channels

Voltage-dependent calcium channels play a fundamental role in the intestine and in pharmacological management of IBS. These ionic channels mediate calcium influx in response to membrane depolarization, and they regulate intracellular processes such as contraction, secretion and neurotransmission in a variety of cells. (21) Calcium channels are classified by their properties and pharmacology. They include L-type calcium channels (long duration). They are high conductance channels that produce long-lasting depolarization and which are inhibited by dihydropyridine derivatives (DHP). (22, 23) Currents associated with this type of channel are important for muscle and endocrine cells in which contraction and secretion of substances are mediated. (21)

Type N (neuronal) currents are also durable, but require strongly negative potentials for complete elimination of inactivation and strong depolarization for activation. (23) Three other channels have been identified in Purkinje cells. Type P currents are blocked by low concentrations of ω-agatoxin, while type Q only responds to high concentrations. Residual currents, which were resistant to all known calcium blockers at the time of their discovery, were called type R (resistant). Type T (transient) voltage-dependent calcium channels are characterized by small and transient conductance activated by weak depolarization. (23) These currents are responsible for modulating the action potential and the performance of pacemakers.

In the 1980s DHP antagonists became the first calcium antagonists to be used medically. They block L channels and are used to treat hypertension by exploiting their properties as vasodilators. (22) Calcium antagonists have no effect on skeletal muscle, but they can have some influence

on heart muscle through reduction of activity and conduction of pacemakers. Because IBS includes abnormal gastrointestinal motility, calcium antagonists used for cardiovascular disease appear to have potential for relieving symptoms by relaxing the smooth muscles of the colon. Nicardipine, which has spasmolytic properties, was proposed as a possible IBS treatment in the late 1980s. (24) However, cardiovascular side effects have seriously limited the application these calcium antagonists. This led researchers to search for other substances that act selectively within the gastrointestinal tract.

ANTI-SPASMODIC DRUGS

These medications act by inhibiting the action of acetylcholine on muscarinic receptors or by blocking calcium channels in the gastrointestinal smooth muscle. As a class, antispasmodics have been used in the treatment of IBS for many years. They treat the subgroup of IBS patients who have abnormal contractility of the gastrointestinal smooth muscle and altered gastrointestinal transit which contribute to pain and altered bowel habits. (25)

Otilonium Bromide

Otilonium bromide's structure consists mainly of quaternary ammonium, so it is weakly absorbable from the gastrointestinal tract. Experimental studies show that it accumulates in the walls of the gastrointestinal tract after oral administration and is almost completely excreted in feces. (25) Otilonium bromide not only blocks L-type and T-type calcium channels, but also the M1, M2, M4 and M5 muscarinic receptors. The antagonistic effects of otilonium bromide on the M3 coupled calcium signaling pathway in human colonic crypt cells suggests antisecretory action in patients who have the diarrhea type of IBS. Antagonism of neuroquinine-2 receptors (NK-2) also causes spasmolysis while reducing peripheral sensory afferent transmission to the central nervous system, possibly contributing to greater efficacy. (26, 27) These effects suggest that otilonium bromide may be effective at reducing spasms and abdominal pain, the two main symptoms of IBS. (2)

Otilonium bromide has been evaluated for management of abdominal pain in IBS patients in a clinical trial. Patients diagnosed according to the Rome II criteria were randomly assigned to case and control groups. They received either 40 mg of ethyl bromide or a placebo three times a day for 15 weeks. Patients who took otilonium bromide had less frequent pain, bloating and bowel movements than did the control patients who took placebos. The outstanding result of this study was that otilonium bromide significantly reduced the frequency of abdominal pain from more than half of the days to less than one day per week while the patients who took placebos continued to have one to three episodes per week. During the 10-week follow-up period after the end of treatment, the likelihood of recurrence of symptoms was significantly higher in the placebo group than in the otilonium bromide group. (28, 29) This finding may be explained by the prolonged persistence of ethyl bromide in the colon wall due to its lipophilic properties. (25)

Among the most commonly reported side effects associated with the use of ethyl bromide are dry mouth, nausea, and dizziness. These may be caused by peripheral and central muscarinic antagonism and may be explained by the known ability of otilonium to bind muscarinic receptors. (27)

Otilonium bromide has been evaluated in 5 randomized controlled studies which included a total of 791 patients. (29-33) A metaanalysis found evidence of a beneficial effect [risk ratio (RR) = 0.70, 95% confidence interval (CI): 0.54-0.90; number needed to treat (NNT): 5, 44% CI, p = 0.13], but there was borderline heterogeneity among study results (I^2 = 44%, p = 0.13). The Colombian Association of Gastroenterology (Asociación Colombiana de Gastroenterología - ACG) clinical practice guidelines strongly recommends the use of ethyl bromide for increasing the frequency of overall improvement of symptoms in IBS patients but the quality of evidence is still low.

Pinaverium Bromide

Pinaverium bromide, a derivative of quaternary ammonium, is poorly absorbed and has pronounced pharmacological effects in the gastrointestinal tract rather than in cardiovascular system. (34) Its gastrointestinal absorption rate is low and is characterized by hepatobiliary excretion. (35) Its effects are very similar to those of established L-type calcium channel blockers (nitrendipine, diltiazem) since it reduces the plateau phase of slow waves which inhibits calcium influx and prevents subsequent contractions. (36)

It has also been shown to inhibit the acetylcholine (ACh)-induced contractile response of smooth muscle in dog and rat colons. Acetylcholine is a neurotransmitter of the intrinsic cholinergic nerves. (36) Similarly, in smooth muscle cells of the colon isolated from normal or inflamed human colons, it inhibits contraction induced by other agonists (CCK). (37) The involvement of sensory afferent neurons in IBS has been demonstrated, and this could also explain the efficacy of pinaverium bromide for treating motility disorders and intestinal hypersensitivity, two key IBS symptoms.

A pilot study of 12 IBS patients has used surface electromyography to study how treatment with pinaverium bromide affects colonic motility. Surface electromyography was used during a two hour fasting period and a postprandial

period of two hours after a standard meal prior to and after 10 days of treatment with 50 mg of pinaverium bromide taken three times a day. Principal IBS symptoms including abdominal pain, bloating and impaired bowel habits began to improve on day 4 of treatment. Abnormal patterns of colonic motility including greater frequency, greater extent of contractions and impaired rhythm in motor activity decreased after 10 days of treatment. A continuation of that study included 22 IBS patients and 7 healthy controls. (38) Healthy controls received no treatment, but served as controls for electromyographic measurements. The study protocol was as described above, except the duration of pinaverium bromide therapy was extended to 14 days. The results showed that fasting and postprandial colonic motility parameters in IBS patients improved in relation to controls. These symptoms were effectively reduced in 14 days of pinaverium bromide therapy. Abdominal pain and bloating also improved significantly with treatment.

Adverse effects that have been described include hypersensitivity, angioedema, constipation, drowsiness, dysphagia, epigastric pain, erythema, headache, nausea, pruritus, vertigo, vomiting and xerostomia. The use of pinaverium bromide has generally been considered safe although its use is contraindicated in pregnant women. Although there are insufficient animal reproduction studies and no information on human pregnancies is available, there is a theoretical risk of sedation and hypotonia in newborns if pinaverium bromide is used at the end of pregnancy. However, no cases have been reported.

Evaluation of pinaverium bromide by four studies with a total of 615 patients found a statistically significant improvement of IBS symptoms (RR = 0.56; 95% CI 0, 38-0.82) with a NNT of 4 (95% CI 3-6) although the studies heterogeneity was statistically significant (I2 = 61%, p = 0.05). (39-42) The ACG's clinical practice guidelines strongly recommends pinaverium bromide for reducing abdominal pain in IBS patients although the quality of evidence is still low.

Trimebutine

Trimebutine [3,4,5-trimethoxybenzoic acid 2 (dimethylamino)-2-phenylbutyl ester] has multifaceted modes of action. Its spasmolytic activity is unique, and it has significant non-selective agonist activity for the μ, κ and δ intestinal opioid receptors. Trimebutine has been reported to prematurely induce phase III of the migratory motor complex of the intestine, and it has also been shown to modulate visceral sensitivity. It probably acts on smooth muscles, enteric nerves, and the interstitial cells of Cajal which are key for initiation and regulation of gastrointestinal motility. Some studies have reported that trimebutine acts as a regulator of the Ca2 + and K + channel in the intestine. (43)

A multicenter, randomized, double-blind, non-inferiority clinical study of 197 patients has compared fenoverine with trimebutine. Subjects were randomized to receive 100 mg of fenoverine three times a day or 150 mg of trimebutine three times a day for 8 weeks. The primary evaluation criterion was the proportion of patients who experienced a 30% reduction of baseline abdominal pain by week eight as measured by the scale of intestinal symptoms. (44)

Assessment criteria were changes in abdominal distension, diarrhea, constipation, and general satisfaction scores. Fenoverine was found to be not inferior to trimebutine at week eight (treatment difference, 1.76%; 90% CI: 10.30 to 13.82; p = 0.81). Fifty-four of seventy-eight patients (69.23%) who took fenoverine and 56 of 83 patients (67.47%) who took trimebutine had 30% reductions in abdominal pain or discomfort compared to the baseline. (44)

There have been two systematic reviews that compared trimebutine to placebos for IBS patients. Both systematic reviews showed greater improvement of abdominal pain with trimebutine treatment than with placebos, but the difference was statistically significant in only one of the reviews. That systematic review was based on three randomized controlled trials. It found an RR of 1.32 with a 95% CI of 1.07 to 1.64. The difference in the other systematic review was not statistically significant. Its odds ratio (OR) was 1.28 with a 95% CI of 0.53 to 3.14. (45)

A systematic review based on two randomized controlled trials found that trimebutine's overall evaluation was not significantly better statistically than was the overall evaluation of placebos (RR: 0.97; 95% CI: 0.68 to 1.38; OR: 1.27; 95% CI: 0.58 to 2.79). Another systematic review based on a randomized controlled trial reported that there was no statistically significant difference in adverse events between trimebutine and placebos (OR: 0.62; 95% CI: 0.20 to 1.88). (45)

Another randomized controlled trial reported that clinical recovery was observed in 94.9% of patients treated with trimebutine. Spontaneous recovery was observed in 20.5% of untreated patients. These findings were based on responses of parents who were asked if their child had adequate relief of pain and discomfort related to IBS in the previous seven days. (45)

Another randomized controlled trial that compared trimebutine with mebeverine found that there was a statistically significant improvement of abdominal pain, consistency and frequency of feces and flatulence compared to the reference values for each drug after six weeks of treatment (p varies between <0.01 and <0.05). However, there were no statistically significant differences in the improvement of symptoms between the two drugs (p values range between <0.23 and <0.71). Compared to baseline, statistically significant symptom improvement was reported for both drugs

after one week of treatment. Quality of life was evaluated with the IBS-QoL questionnaire. It improved statistically significantly after treatment with trimebutine or mebeverine ($p < 0.05$). In addition, patients' improvement was statistically greater with trimebutine than with mebeverine ($p < 0.05$). The authors stated that there were no differences in adverse events between the two drugs, however, no quantitative data were presented. (45)

The ACG's clinical practice guidelines give a weak recommendation for trimebutine for improving abdominal pain in IBS patients although the quality of evidence is still low.

Mebeverine

Mebeverine, a beta-phenylethylamine derived from reserpine, has relatively specific effects on smooth muscle cells without having atropine-like effects in humans. It directly blocks sodium channels and inhibits the accumulation of intracellular calcium, and in experiments with porcine models it was three times more potent than papaverine at inhibiting the ileal peristaltic reflex. Nevertheless, other animal studies of its pharmacology have failed to demonstrate this effect. (2)

An early study by Connell found that intravenous mebeverine decreased all sigmoid colonic motility, especially in hyperactive subjects but had less or no effect on hypoactive subjects. Mebeverin was superior to placebos in a 12-week study of treatment in IBS patients in terms of symptom improvement and overall well-being. Mebeverin prolonged ambulatory manometry in 12 IBS patients and 6 healthy controls, compared to placebos, and mebeverine had no significant effects on the motor complex of the small intestine. In contrast, a higher phase 2 motility index was observed in both diarrhea-type IBS and in constipation-type IBS. The phase 3 motility index was also affected. These alterations in the motor activity of the small intestine by mebeverine suggest possible spasmolytic and prokinetic effects in IBS patients. (2)

Positive results have also been obtained in studies of control of symptoms in IBS that did not compare the drug to placebos. Significant improvement with a minimum number of adverse events was observed after 6 weeks of treatment with simple and sustained forms of mebeverine. A comparison of pinaverium bromide to mebeverine in 91 patients with diarrhea-type IBS found that improvements in overall well-being were similar in both groups: frequency of defecation decreased markedly, consistency of bowel movements improved in both groups, and no significant side effects were observed. A clinical trial that compared the effects on diarrhea type IBS of ramosetron, a 5-HT3 antagonist receptor, with those of mebeverine found that both treatments were equally effective in reducing pain, discomfort and urgency, with improvement of Bristol stool scale scores and frequency of bowel movements compared to the baseline. (2)

Nevertheless, results have been controversial in comparisons of the effects of mebeverine with placebos and another medication and results have been measured by self-control. A recent systematic review which included eight randomized trials found that clinical improvement and abdominal pain relief with mebeverine were not statistically better than the results from placebos. No differences were found between the effectiveness of 200 mg and 135 mg doses of mebeverine. Tolerability was excellent, and there were no significant adverse effects. Similarly, mebeverine was not found to have better results than placebos in a study in 135 IBS patients recruited from general practice who met the Rome III criteria. Mebeverine, methylcellulose and placebos were compared with or without combination with cognitive behavioral therapy. (2) However, a study conducted in London found that cognitive behavioral therapy sessions plus mebeverine were beneficial and that symptom relief and reduction of social and labor disability persisted for up to 6 months after therapy. Depression and anxiety predict poor outcomes for IBS patients treated with mebeverine, but in cases of patients with behavioral disturbances such as avoidance the combination of mebeverine with cognitive behavioral therapy may be useful. (2)

The clinical practice guidelines published by the ACG give a weak recommendation in favor of the use of mebeverine for treating IBS due to low quality of evidence.

In conclusion, the individual effect of antispasmodics has been difficult to interpret since there are only a small number of studies evaluating each medication. Nevertheless, these studies have found that antispasmodics are more effective treatments of IBS than are placebos. Of the medications studied, otilonium and pinaverium are quaternary derivatives of ammonium which are poorly absorbed in the gastrointestinal tract. They act primarily at the local level by reducing adverse effects of this group of medications and reduce the risk of persistent symptoms significantly more than do placebos.

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