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The Use of Mebeverine in Irritable Bowel Syndrome. A Position Paper of the Romanian Society of Neurogastroenterology based on Evidence

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder associating abdominal pain or discomfort with a modified bowel movement pattern regarding stool frequency and consistency [1]. It is a common disorder, affecting 10% to 20% population worldwide [2-4], including Romania [5]. It causes not only physical symptoms, but emotional and social functioning also [6], impairing the quality of life (QOL) [7-9].

The pathophysiology of IBS is not entirely decrypted, but evidence of multiple pathogenic pathways has been assumed [10]: abnormal motor function due to visceral hypersensitivity or autonomic dysfunction [11-14], or intervention of psychological factors indicating an impairment of enteric nervous system and brain–gut axis [15, 16].

Concerning the predominant bowel pattern, IBS patients are subgrouped as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed IBS (IBS-M), or un-classified IBS [1]. This classification is useful for clinical practice and therapeutic strategies, but frequently patients change from one subtype to another in time ("alternators") [17, 18].

The role of pharmacotherapy in IBS is limited and oriented mainly towards symptom control [1]. Many of the available treatments are not overall accepted by medical payers and patients [19].

Although newly developed drugs targeted on receptors are emerging, of which some are already in use, antispasmodic treatment remains a powerful therapeutic tool for IBS [20]. The aim of this position paper was to develop a useful tool for primary care physicians and specialists, that would encompass the needs of physicians, investigators, insurance and regulatory bodies. Furthermore, it should be representative and relevant for the Romanian medical community.

METHOD

The main steps in the process of this consensus were: 1) selection of the working group; 2) establishing the working flow; 3) development of draft statements; 4) a systematic literature review to identify the evidence to support the statements, and 5) grading of the evidence.

1) The members of this working group were selected on account of their expertise/knowledge in IBS, evaluated by the research interest expressed by published papers and/or participation at national or international conferences. The working group consisted of nine experts, members of the Romanian Society of Neurogastroenterology (RSNG). They all had had experience for at least 15 years as practitioners, teachers and investigators of functional gastrointestinal disorders. A PhD student working in IBS (A.C.) was added to this group and was charged mainly with the networking and secretarial activity.

2) The working group decided to elaborate a number of questions to be answered according to available references and experience (where necessary). The next steps were the identification of pertinent references and the selection of those to be included in this review. All members of the consensus group proposed their own list of papers and the first author had to mediate in case of differences. However, no such negotiation was necessary, as there was unanimous agreement about the papers included in the analysis. Further, statements were elaborated by

the authors and circulated between all the contributors; all of them agreed with the final version of this paper.

3) The following questions were addressed, requiring statements: Are antispasmodics useful in IBS? How does mebeverine act (pharmacology and pharmacodynamics)? Is mebeverine useful in IBS? What is the effect of mebeverine on the QOL of IBS patients? Which one of the pharmaceutical forms of mebeverine is better? Can mebeverine be associated with other therapies? Are there Romanian data on the effect of mebeverine in IBS? The group developed the initial statements and reviewed the evidence to support the statements that were presented.

4) In order to identify the studies of interest, the literature was searched using a strategy that included the terms "mebeverine", "mebeverine and irritable bowel syndrome" from the MEDLINE and Cochrane databases. Selection criteria were broad, for gathering the relevant studies for the purpose of the research. The search was limited to articles published in English, French, Spanish or German. The title and the abstract of the studies identified by of the computerised search were scanned to exclude the irrelevant ones. The full text of the remaining studies was gathered through on-line access or from the Library of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca.

5) The evidence was graded according to the usually accepted system [21].

SEARCH RESULTS

Our initial search on MEDLINE and Cochrane databases yielded 155 results using "mebeverine" strategy. In a more detailed search using "mebeverine and irritable bowel syndrome" strategy (28 September 2014) 54 results were retrieved. These were all checked and potentially relevant studies were found. Of the 54 results of the computerised search, a number of 30 papers were not included for various reasons: some were not appropriate for the subject (16) or redundant (8), others were impossible to retrieve / access (6). Full text (where applicable) was read and reference lists were checked in order to find other pertinent data. We identified the studies that met the criteria for our purpose: evaluation of the use of mebeverine.

ANTISPASMODICS IN IBS

Irritable bowel syndrome was also named in the past "spastic colon", meaning that "spasms" cause the algic symptomatology [22]. Current recommendations for the treatment of IBS still advise antispasmodics to reduce pain or discomfort severity though this class has been used for decades for treating IBS [22, 23]. Antispasmodics are the most frequently prescribed drugs in IBS; in pain-predominant cases these agents are the initial recommended therapy [20]. Antispasmodic agents are more accessible and their use is more extensive in Europe compared to the USA [24].

The antispasmodics include several drug classes: smooth muscle relaxants, antimuscarinic agents, anticholinergics, ammonium derivatives with calcium channel blocking properties, peripheral opiate agonists [20, 23]. A meta-analysis published in 2001 shows that smooth muscle relaxants are efficient in diminishing abdominal pain and also global symptoms in comparison to a placebo [25].

Although antispasmodic agents remain among the most widely and commonly prescribed drugs for IBS, there is limited clinical evidence to support their use [23]. The American College of Gastroenterology (ACG) IBS task force performed an evidence-based comprehensive and extensive systematic review on IBS [20, 23]. According to this, some antispasmodics (hyoscine, cimetropium and pinaverium) could provide for short-term alleviation of abdominal pain or discomfort in IBS (Grade 2C), but evidence for long-term efficacy is not available (Grade 2B) and for safety and tolerability evidence is also limited (Grade 2C) [23]. Although there appears to be a superiority of peppermint oil over placebo in IBS, the conclusion was reached only in a limited number of studies (Grade 2B) [23].

Although there is a level II evidence suggesting that antispasmodics may alleviate abdominal pain, a systematic review published in 2006 found a paucity of clinical trials to support their effect on global symptoms and insufficient trial data to assume relative efficacy of the different agents or classes of agents [24]. These conclusions are similar to those of a Latin American review [22] and of the ACG [23].

Antispasmodics are suitable for long-term treatment as well as for short-term and single use [26]. The anticholinergic properties of some of these agents can lead to side effects i.e. dry mouth, dizziness, confusion (particularly in the elderly), blurry vision, urinary retention and constipation [20].

Due to the fact that mebeverine has no anticholinergic properties, it has no atropinic side effects and can also be used in the elderly.

MEBEVERINE AND IBS

A meta-analysis indicates a superior effect ($p < 0.001$) of antispasmodic treatment for abdominal pain and improvement of the global assessment vs. placebo [27]. Another study compared mebeverine 135 mg three times daily (tds) plus dietary advice vs. mebeverine 135 mg tds plus ispaghula 3.5 g twice a day (bid) or tds and showed the improvement of pain and transit of both associations vs. baseline [24, 28].

Antispasmodic agents were found in another meta-analysis to be superior compared to placebo for treating IBS, with almost no significant adverse events [29].

A trial evaluating colonic transit after pinaverium 50 mg tds or mebeverine 100 mg tds showed a significant improvement in stool consistency in both groups at 2 weeks ($p < 0.01$), with a significant reduction in daily defecation frequency ($p < 0.05$), as well as an improvement in global wellbeing [30].

Otilonium bromide was compared with mebeverine in Asian patients with IBS [19]. The study concluded that in Orientals, otilonium bromide is as effective as mebeverine for relieving IBS symptoms. Ramosetron when compared to mebeverine in male patients with IBS-D showed similar effects regarding the severity scores of abdominal pain/discomfort and urgency, stool frequency and stool form score, which were significantly reduced by both drugs in comparison with the baseline, with no significant differences between the groups [31].

Another trial compared alosetron, a selective 5-HT3 receptor antagonist, and mebeverine in non-constipated IBS females. Alosetron was more effective than mebeverine in reducing abdominal pain and discomfort ($p = 0.001$ in the second month of treatment) [32].

A study including 89 patients and looking for the long-term outcome reported clear improvement in terms of abdominal pain and flatulence after 4 weeks of treatment, effect which was maintained for the 12 months of the study [33]. An open-label, multicentric, 8-week, phase IV study, including 318 patients aged 18–53 years with IBS, indicated at 8 weeks improvement in more than 48% of all patients, irrespective of the type of presenting symptoms. Improvement continued throughout the 8 weeks of the study, justifying prolonged treatment in order to obtain maximum benefits. This study demonstrates that mebeverine influences GI motility, as 48-73% responders indicated a good response in each of the different subgroups [34].

MEBEVERINE AND QOL IN IBS

Irritable bowel syndrome can have a considerable impact on the QOL [35]. It affects sleep, sexual functioning, leisure, diet, depression, anxiety, employment and travel [36].

In an open label study, IBS patients were treated in primary care for 8 weeks with mebeverine. The QOL score was significantly improved, by 44%, and the mean symptom score by 66% ($p < 0.001$). Improvement in the symptom score and QOL was significantly higher in patients who perceived a closer association between stress and symptomatology ($p < 0.001$). Optimum results for mebeverine treatment were observed in patients with stress-induced symptoms, a short history of IBS, alternating stool habits, younger age and first time users of mebeverine. No differences were seen regarding gender [37].

Another recent prospective observational cohort study showed that the treatment with mebeverine hydrochloride (or with pinaverium) improved the QOL [38].

Mebeverine and trimebutine (used for comparison) were recently (2014) found to improve significantly (p-value not shown) the mean QOL scores after 6 weeks of treatment [39].

Irritable bowel syndrome patients who experienced maladaptive behavior (e.g. avoidance behavior) and had received mebeverine plus cognitive behavior therapy (CBT) treatment, perceived less disability after 12 months, suggesting that CBT treatment was effective in modifying the maladaptive coping behavior (e.g., avoidance behavior) associated with mebeverine [40].

MEBEVERINE – STANDARD FORM OR MODIFIED RELEASE FORM

A multicentric, randomised, double dummy, double-blind study aimed to demonstrate the equivalence of two forms of mebeverine hydrochloride: the 200 mg bid capsules and 135 mg tds tablets in IBS in the treatment of abdominal pain, proving statistically the therapeutic equivalence (difference < 18%; $p = 0.003$) of the two forms with no safety concerns identified [41].

A similar conclusion was drawn by a study that compared mebeverine 200 mg, the modified release capsule, with the 135 mg plain tablet of mebeverine [42]. The former has the extended release properties, characterized by pharmacokinetic properties and has an optimal bioavailability [42]. The conclusion was that the twice-daily dosage regimen of the 200 mg modified release capsule was a good alternative to the three times daily dosage regimen of the 135 mg plain tablet, because the reduced daily intake was likely to benefit patient compliance [42].

A systematic review concluded that mebeverine 200 mg is as effective as mebeverine 135 mg regarding clinical improvement as well as relieving abdominal pain, indicating no major adverse effects for mebeverine 200 mg and also no greater incidence of adverse effects in comparison to mebeverine 135 mg [43]. By reducing the number of the daily doses from three to two, the mebeverine slow-release (SR) capsules are preferred in terms of patients' compliance [43].

MEBEVERINE IN ASSOCIATION WITH OTHER TREATMENTS

A number of studies compared the association of multiple treatments. One of the studies concluded that mebeverine with bran and lorazepam seemed to be not more effective than lorazepam; on the other hand, the combination of mebeverine with ispaghula husk and fluphenazine hydrochloride appeared very efficient [44].

Besides pharmacological therapy, diet and lifestyle changes are important in IBS [45]. According to a previous guideline, antispasmodics should be prescribed in IBS, considering also dietary and lifestyle advice [46].

Due to the redundance of mechanisms regulating multiple gut functions: neuromuscular, neurosensory, and neuroimmune, and also taking into consideration the multifactorial pathophysiology, it is conceivable that an efficient treatment for functional gut disorders might necessitate a mixed or a combined therapy [47]. This is sustained also by a meta-analysis which found that by adding simethicone, the effect was superior to that of the antispasmodic by itself, suggesting that the combination of an antispasmodic with another agent - an anti-foaming agent - may represent a novel therapeutic option [29].

Very recent data from a preliminary study showed that the combination of mebeverine with a probiotic and a glutamate reuptake enhancer that is also a n-methyl d-aspartate receptor antagonist induced a significant improvement of the overall standard GI symptom rating scale ($p=0.02$) compared to the combination of mebeverine and a probiotic or mebeverine, probiotic and amitriptyline [48].

We might add also that individualizing therapy is crucial for optimal response.

MEBEVERINE IN ROMANIA

In Romania, mebeverine is widely prescribed, although no published trials exist. The drug is available under two pharmaceutical forms, as SR 200 mg capsules (enteric coated microspheres) and as 100 mg dragees. Because adherence to treatment is crucial, by reducing the number of daily doses of mebeverine from three to two, the mebeverine SR capsules

have an advantage over the 100 mg dragees in terms of patients' compliance. The evidence gathered in different international trials (see above) supports the use of mebeverine in IBS.

CONCLUSIONS

This paper documents the current evidence of mebeverine treatment in IBS. Mebeverine relieves IBS symptoms by reducing mainly the intensity of abdominal pain and also the flatulence and the disturbed bowel movements (diarrhea/constipation) with almost no serious adverse events and a significant improvement in the quality of life.

Conflicts of interest: D.L.D., S.B., M.D., V.D., A.G. and I.S. were speakers for Abbott Company at local symposia. The company was not involved at any stage in the manuscript preparation of this Position paper.

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