

## EFFICIENCY OF ANTISPASMODIC DRUGS IN THE IRRITABLE BOWEL SYNDROME

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### Abstract

*The authors re-evaluate the antispasmodic treatment in the Irritable Bowel Syndrome (IBS). The main therapeutic option, the benefits and the limits of current therapies are analyzed.*

*Despite many published study results, the number of the patients included in the trials is low and not all the Rome diagnostic criteria were followed. There are hopes for new randomized clinical trials to evidentiate the superiority of one therapeutic agent in the global improvement of the IBS symptoms.*

**Keywords:** Irritable Bowel Syndrome, antispasmodic, anticholinergic.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized mainly by abdominal pain and altered bowel habits, in absence of the organic pathology. In time, many terms were used such as: irritable colon, spastic colon, nervous colon.

The diagnostic criteria have evolved in time, in order to incorporate new information about this complex disorder. The changes made to the old classification Rome II are referring to:

1. Introduction of a frequency threshold of symptoms;
2. The duration of symptoms until the diagnosis;
3. Redefining of IBS symptoms.

Currently Rome III Diagnostic Criteria for IBS [1] are accepted:

1. At least 3 months until onset at least 6 months previously of recurrent abdominal pain or discomfort associated with two or more of the following:
  - Improvement with defecation; and/or
  - Onset associated with a change in stool frequency; and/or
  - Onset associated with a change in form (appearance) of stool.

The symptoms of IBS are based on stool consistency: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS mixed type (IBS-M) and IBS not subtyped (IBS-U). The subtyping is important to explain the physiopathologic mechanism and in the treatment association.

The pathophysiology of IBS is considered multi-factor, generated by a complex of genetic, psychosocial and environment factors with a negative impact on patient life quality.

The IBS management is done in steps:

1. Diet and lifestyle advice;
2. Pharmacological therapy:
  - Antispasmodic agents;
  - Prokinetics;
  - Tricyclic antidepressants;
  - Selective serotonin reuptake inhibitors.
3. Psychological interventions:
  - Cognitive behavior therapy;
  - Psychological therapy;
  - Hypnotherapy.
4. Complementary and alternative medicine:
  - Acupuncture;
  - Reflexotherapy.

Self-medication with over-the-counter laxatives, antidiarrhetics is common, but the majority of the patients require drug prescriptions with antispasmodic followed by prokinetic agents. According to a French survey almost half of IBS patients using medication considered their treatment ineffective [3].

How to orient in practice? How do we choose? The treatment objectives are:

1. Symptoms improvement (pain, discomfort, bloating, constipation, diarrhea);
2. Ameliorate the global assessment of symptoms of IBS
3. Improve the quality of life

Antispasmodics can be classified in three major subclasses:

1. Anticholinergic / antimuscarinic agents:
  - Dicyclomine Hydrochloride
  - Hyoscyamine Sulfate
  - Cimetropium Bromide
  - Otilanium Bromide
  - Octylonium Bromide
  - Prifinium Bromide

Acceptat în data de: 04.10.2010

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- Zamifenacin
  - Darifenacin
2. Smooth muscle relaxants:
    - Mebeverine
    - Papaverine-like agents
  3. Calcium channel blockers:
    - Pinaverium Bromide

Generally these agents have mixed pharmacological properties. They reduce pain through inhibition of contractile pathways in the muscle wall.

There is a limit to the action of anticholinergic agents at the interstitial level. They do not cancel completely the vagal stimulation effects because some of the postganglionic fibers from the myenteric plexus do not use acetylcholine as neurotransmitter but other neurotransmitters such as serotonin and dopamine.

The anticholinergic effects on the digestive tract are known: decrease of motility, increase of sphincter tonus and decrease the intestinal secretions.

In the United States the antispasmodics **Dicyclomide** and **Hyoscyamine** are available for IBS.

**Cymetropium Bromide** is a muscarinic compound with strong antispasmodic activity. In a clinical trial [4], Passaretti has demonstrated that cymetropium bromide 3x50 mg /day shortened the whole gut transit time and improved the global clinical condition significantly compared with placebo.

**Otilonium Bromide (OB)** is a quaternary ammonium compound with a potent smooth muscle relaxant activity. Evangelista [5] has confirmed the high tropism of OB for the gastrointestinal tract after oral administration of 2 mg / kg, <sup>14</sup>C-OB was taken up by the intestinal wall and negligible concentrations were found in other tissues.

In clinical studies the standard therapeutic dose was 3x40 mg daily.

In a meta-analysis, Peynard [6] ranked OB in a good position in the treatment of IBS using global assessment, pain improvement, abdominal distension and absence of side effects as endpoints.

The principal mechanisms of OB action are:

- Inhibits smooth muscle contraction both in vitro and in vivo preparations;
- Shows selectivity for the different segments of the intestinal tract;
- Interferes with intracellular and extracellular Ca<sup>++</sup> fluxes;
- Is active in different models of gut stimulated hypermotility.

**Spasmomen** is the commercial designation of the Romanian market product, sold as 40 mg tablets.

Recent research on intestinal physiology has led to the identification of new target receptors. The latest generations of anticholinergic drugs (**Zamifenacin**, **Darifenacin**) have selective antagonism on type 3 muscarinic receptors.

**Mebeverine** is a moderate action antispasmodic agent with tropism for musculature. The superiority of Mebeverine over antimuscarinic agents is its relative selectivity for smooth intestinal muscle and the absence of anticholinergic effects. A recent meta-analysis suggests that, based on global improvement, Mebeverine is a little better than placebo.

On the Romanian market there are Colospasmin pills of 100 mg, Duspatalin delayed release capsules of 200 mg (the recommended dosage is one capsule twice a day before meals).

There are few studies in the medical literature cited for the efficacy of **Pinaverium Bromide** in IBS. Awad [7] demonstrated that a dose of Pinaverium Bromide of 50 mg t.i.d. diminished the pain duration from several hours to a few minutes. The medicine is safe and produces a significant benefit in the quality of the patient's life.

A competent meta-analysis and a judgmental evaluation of antispasmodic agents indications in the irritable bowel syndrome treatment is performed by Tack [4].

According to Tack, the antispasmodics are in widely available and used more extensively in Europe than in the USA. He is making also an assessment of clinical trials in this area, most of them being of low to intermediate quality, included small numbers of patients and did not use Rome diagnostic criteria in all the cases.

9 out of 12 studies showed that antispasmodics provided a statistically significant improvement in abdominal pain compared with placebo. Only three studies provided evidence of an improvement in global IBS symptoms and only two studies reported a significant improvement in bowel function vs. placebo [4].

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