THERAPY OF DIARRHEA IN IRRITABLE BOWEL SYNDROME

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Abstract

Irritable bowel syndrome (IBS) became in the last years a multifactorial disease involving brain – gut connections, visceral hypersensitivity, intestinal inflammation and increased intestinal permeability, and alteration of the gut microflora. In spite of progress regarding IBS pathogenesis, the treatment is non-standardized and with inconsistent results. Treatments should incur limited side effects; so far none of them are efficient in all cases. Currently there are three treatment options – dietary, pharmacological, and psychological. There are no specific dietary recommendations to improve diarrhea in patients with IBS. Nevertheless, several options have been tried out: administration of partially hydrolyzed guar gum, exclusion diet based on IgG antibodies to food, administration of herbal preparations. Various pharmacological agents have been also tried in the management of IBS – antispasmodic agents, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin receptor antagonists, anti-diarrheal agents, antibiotics and probiotics. Psychological treatment is based on the assumption that IBS symptoms are a response to stressful life events or daily hassles, producing maladaptive behaviour and inappropriate symptom attributions. Due to the lack of panacea for IBS, a good strategy is to start with the most simple drugs (i.e. antispasmodic) and probiotics, trying in the same time to reduce daily hassles. Loperamid, diosmectite and alosetrone may be efficient in severe cases.

Keywords: irritable bowel syndrome, diarrhea, pharmacological therapy.

Irritable bowel syndrome (IBS) became in the last years a multifactorial disease involving brain – gut connections, visceral hypersensitivity, intestinal inflammation and increased intestinal permeability, and alteration of the gut microflora. The diagnostic of IBS is based on the presence of abdominal pain or discomfort which is clearly linked to bowel function, being either relieved by defecation or associated with change in stool frequency or consistency. The former suggests a colonic origin and the latter suggests a link to changes in intestinal transit, which might reflect changes in either motor patterns or secretion. Symptoms that are common in IBS include bloating, abnormal stool form (hard and/or loose), abnormal stool frequency, straining at defecation, urgency, feeling of incomplete evacuation, and the passage of mucus per rectum [1].

Regarding the stool patterns, the Rome II classification used a complex multidimensional set of criteria which included stool frequency, stool consistency, urgency, and straining. Both straining and urgency can be seen with both hard and loose stools, which can also be associated with both frequent and infrequent defecation. The Rome III sub-classification is based solely on stool consistency. Patients with loose stools (types 5, 6 and 7 in the Bristol Stool Scale) more than 25% of the time and hard stools less than 25% of the time are defined as „IBS with diarrhea" (IBS-D) patients [1,2]. Patients with hard stools more than 25% of the time and loose stools less than 25% of the time are defined as „IBS with constipation" (IBS-C). About one third to one half of IBS patients are „IBS-mixed" (IBS-M), who describe both hard and soft stools more than 25% of the time, with a small (4%) unclassified (IBS-U), with neither loose nor hard stools more than 25% of the time. Those whose bowel habit changes from one subtype to another during follow up over months and years are termed „alternators" [1,2]. Bristol stool scale classifies the form of human faeces into seven categories listed below [3].

Type 1: Separate hard lumps, like nuts (hard to pass)

Type 2: Sausage-shaped, but lumpy

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Type 3: Like a sausage but with cracks on its surface

Type 4: Like a sausage or snake, smooth and soft

Type 5: Soft blobs with clear cut edges (passed easily)

Type 6: Fluffy pieces with ragged edges, a mushy stool

Type 7: Watery, no solid pieces. Entirely liquid

Irritable bowel syndrome is a non-fatal chronic condition, and in a lot of cases, especially in patients with IBS with diarrhea, determines the impairment of quality of life in all its aspects. Treatments should incur limited side effects; so far none of them are efficient in all cases.

1. Dietary treatment

Two-thirds of patients with IBS perceive their symptoms to be diet related [4] and restrict their food intake hoping to improve symptoms. These patients will always be concerned what they should and shouldn't eat, being very attentive to dietary advices. Some of them are at risk of low nutrient intakes [5]. Foods rich in carbohydrates, as well as fatty food, coffee, alcohol and hot spices were most frequently reported to cause symptoms. Gas problems and abdominal pain were the most frequently reported symptoms [4].

1.1. Alterations in fiber intake

A diet enriched with fibers is a frequent recommendation in IBS-C patients, but in a lot of cases (up to 55%) this diet can increase the severity of bloating and abdominal discomfort [6]. Some studies report that soluble fibers, such as partially hydrolyzed guar gum (PHGG), have therapeutic benefits. PHGG decreased symptoms in constipation-predominant and diarrhea-predominant forms of IBS, decreased abdominal pain and improved the quality of life [7]. Current recommendations are that if it is felt that fiber supplementation is needed and this cannot be achieved by diet alone, then the soluble varieties (ispaghula, sterculia, or methyl cellulose) are probably the best choice [8].

1.2. Role of food allergy and exclusion diets

Patients with irritable bowel syndrome often feel they have some form of dietary intolerance and frequently try exclusion diets. The mechanism could be an increased intestinal permeability with food allergens entering the intestinal wall and interacting with immunocompetent cells. Nevertheless, food allergies are rare, and for that sub-group of patients, the exclusion diet is helpful. Dietary exclusion would be much easier if there was a simple test that could be used to predict which food, or foods, are likely to be causing problems. The results of an exclusion diet are better when food elimination is based on IgG antibodies to food and not only based on patients' reports [9]. A diet without fibers determined in a small study a significant decrease in hydrogen and methane production by the intestinal microflora, with improvement of bloating and abdominal pain. The effect was as strong as the one observed after metronidazole administration [10].

1.3. Carbohydrate intolerance

The prevalence of sugar malabsorbtion is underestimated in IBS patients, fructose and sorbitol being incorporated in a lot if industrial products. Their malabsorbtion determines an increased gas production and symptoms similar to IBS. Some studies reported improvement of all symptoms for the majority of patients (74%) after exclusion diet, in patients with IBS and fructose malabsorbtion on breath hydrogen testing [11]. To date, there is no sufficient evidence to justify an exclusion dietetic regimen for a majority of IBS-D patients [12].

1.4. Treatment with herbal preparations

A German team conducted in 2004 a double-blind, randomized, placebo-controlled, multi-centre trial, testing the efficacy of a commercially available herbal preparation (nine plant extracts) and a research herbal preparation (five plant extracts) versus placebo. Both were significantly better than placebo in reducing the total abdominal pain score and the irritable bowel syndrome symptom score at 4 weeks. Diarrhea was improved in about 18% of cases [13].

2. Pharmacological treatments for IBS

Various pharmacological agents have been tried in the management of IBS, but these have proved of limited efficacy for the cardinal symptoms of abdominal pain and bloating. Initially the therapeutic target for these symptoms was focusing on relaxing the smooth muscle of the gut, latterly evolving into attempts to alter gut transit and to modulate the perception of visceral afferent information in the CNS. Treatment of bowel dysfunction is comparatively more straightforward, aimed at accelerating or slowing transit as required.

2.1. Antispasmodic agents

The rationale for using antispasmodic agents is to attenuate the heightened baseline and postprandial contractility seen in patients with IBS (particularly when diarrhea predominant). They can reduce colonic motility and gastro-colic reflex during the meals, but efficacy in improving symptoms for example, abdominal pain is low (the number of patients needed to treat in order to obtain a result superior to placebo is 5.5). Three meta-analysis showed that antispasmodic drugs (such as trimebutine, mebeverine, pinaverium) do not improve bowel movement frequency and consistency in patients with IBS [14,15,16].

Other classes of antispasmodic - for example calcium channel blockers and opioid antagonists such as trimebutine - have been shown to produce inconsistent benefit in IBS [8]. Even if the results are not consistent, antispasmodic are used nowadays as first-line drugs in the treatment of IBS. Patients with IBS who have abdominal pain and urgency immediately after food intake, might

benefit the most [12].

2.2. Tricyclic antidepressants

The tricyclic antidepressants are drugs with anticholinergic and non-selective serotonin reuptake inhibitor effects. Tricyclic antidepressants are widely used in other specialties for their ability to potentiate analgesics. The drugs may alter pain perception especially during acute stress. Their effect on visceral sensitivity is still controversial. Five tricyclic agents have been studied (amitriptyline, trimipramine, desipramine, clomipramine, and doxepin) [8]. The effect of these agents primarily relates to pain, and it has been suggested that patients with diarrhea predominant IBS obtain the greatest benefit [17]. Some of the side effects are constipation, dry mouth, drowsiness, and fatigue, and may occur in over one third of patients treated with tricyclic agents. Current recommendations are to start at a dose of 10 mg for any of the tricyclic antidepressants, with a gradual increase to 25 to 100 mg, in the evening. The drug should be continued for 6 to 12 months, after which dose tapering may be attempted [8].

2.3. Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) (i.e. fluoxetine, paroxetine) are widely prescribed and well tolerated in the treatment of anxiety, depression, and somatisation disorders. They are also frequently used in the treatment of irritable bowel syndrome (IBS) although evidence of their efficacy is scarce. Several studies showed global benefit without significant change in bowel symptoms or pain. In a study using citalopram, there was only a modest effect on stool pattern [18].

2.4. Serotonin receptor antagonists (5-HT3 receptor antagonists)

Serotonin is present in large amounts in the enteric nervous system where it acts particularly through the 5-HT3 and 5-HT4 receptors. It is involved in sensory, motor and secretory processes within the gut. It modulates gut motility and the perception of pain and also mediates intestinal secretion [19]. Plasma serotonin concentrations are reduced in IBS patients with constipation and raised in IBS-D, especially those showing postprandial symptoms. These observations support its involvement in the motor and sensory dysfunction associated with IBS [20]. Thus there has been considerable interest in these receptors as possible therapeutic targets for IBS, with agonists at the 5-HT4 receptor predicted to enhance gastrointestinal propulsion (that is, to be prokinetics) [21] and antagonists at the 5-HT3 receptor to slow gastrointestinal transit and reduce visceral sensation [22].

Alosetron, a selective 5-HT3 receptor antagonist was used in the last years for the treatment of female IBS patients with severe diarrhea. Some of its side effects are constipation (in one of for patients treated) and ischemic colitis (1 in a thousand patients treated), and for several years the drug was withdrawn in USA. Meta-analyses showed it to be helpful in women with IBS-D (odds ratio=2.2 (95% CI,1.9 to 2.6). The drug induces relief of abdominal pain and discomfort, and improvement in bowel frequency, consistency, and urgency of bowel movement [23,24], with NNT=7.406. Studies suggest that the benefit continues as long as the drug is taken. The starting dose is 1 mg once daily, which can be increased to 1 mg twice daily after four weeks if the lower dose is well-tolerated but does not adequately control symptoms [25].

Ondansetrone, a selective 5-hydroxytryptamine type 3 receptor antagonist, slows colonic transit in healthy volunteers. In patients with diarrhea-predominant irritable bowel syndrome the stool consistency improved significantly; however, stool frequency, stool weight, abdominal pain, and the symptom criteria for IBS were not significantly altered by the drug [26].

Cilansetron, is another 5-HT3 receptor antagonist which proved to be efficient in patients with IBS-D; phase III clinical trials showed that in 67% of cases there is adequate relief of abnormal bowel habits both in men and women. The drug wasn't approved by the FDA in USA or MRHA in United Kingdom [27,28]. Two Japanese studies showed that ramosetron (5 to 10 mg a day) is active both in male and female patients with IBS-D and is well tolerated [29,30].

2.5. Anti-diarrheal agents

So far, none of these drugs, except for 5-HT3 receptor antagonists, significantly influence stool consistency and frequency. Below are the anti-diarrheal agents used in IBS-D.

The opioid analogues loperamide and diphenoxylate stimulate inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and secretion.

Loperamide is a butyramide derivative and similar in structure to diphenoxylate but does not have opioid activity at standard doses (2-12 mg a day); it also has a more prolonged duration of action and more rapid onset of action than codeine or diphenoxylate. This class of drugs works by inhibiting intestinal secretion and increasing fluid and electrolyte absorption because of prolongation of intestinal transit time [31]. Studies from 1980's showed that Loperamide delays both small bowel and whole gut transit, significantly improves symptoms like diarrhea, urgency and borborygmi. Improvement in diarrhea was associated with reductions in stool frequency, passage of unformed stools and incidence of urgency [32,33].

No such studies have been undertaken with diphenoxylate–atropine (cophenotrope), which is s a derivative of pethidine. Loperamide and cophenotrope can be used both as regular medication and also on demand. The main side effects of loperamide are abdominal pain (especially during the night) and constipation [8].

Codeine phosphate has a potential for dependence when used long-term and therefore should generally be avoided in IBS. Also it induces nausea and dysphoria

[8,31].

Bile acid malabsorption has been variably reported in diarrhea predominant IBS. A recent review showed that 5 studies reported that 10% of IBS-D patients had severe bile acid malabsorption, in 17 studies 32% of patients had moderate bile acid malabsorption, and in 7 studies 26% of patients had mild bile acid malabsorption [34]. Cholestyramine and colestipol are bile salt sequestering agents. For the patients with IBS and diarrhea who have bile acid malabsorption, bile salt sequestering agents seem to be an attractive therapeutical option [31]. The review mentioned above stated that there is a dose-response relationship according to severity of malabsorption to treatment with a bile acid binder: response to colestyramine occurred in 96% of patients with <5% retention, 80% at <10% retention and 70% at <15% retention [34].

Diosmectite (Dioctahedral Smectite) is a natural clay that belongs to the adsorbents group of antidiarrheal drugs. DS is a non-systemic gastrointestinal tract muco-protective agent. Three mechanisms have been proposed for DS's antidiarrheal properties: adsorption of toxin, bacteria and viruses; reinforcement of the intestinal mucus barrier with the reduction of penetration of luminal antigens through the mucus layer and a possible direct modulatory action on proinflammatory cytokine production. Diosmectite (3 sackets daily for 8 weeks) proved to be efficient in reducing symptoms in IBS-D patients [35]. Another study compared Diosmectite (3g twice a day) with loperamid (2 mg twice a day) in chronic functional diarhea and IBS-D, concluding that diosmectite and loperamide are both potent drugs for chronic functional diarrhea [36].

2.6. Antibiotics and probiotics

In the last years, there is an increased interest in the role played by the intestinal microflora not only in the change in bowel habits, but also in the onset and persistence of abdominal pain. Intestinal flora plays a role in intestinal motility and digestive sensitivity. The ecosystem of a patient with IBS can differ from a normal subject. Usually there is a decrease of coliforms, Lactobacilli, and Bifidobacteria, and an increase of anaerobic bacteria, Escherichia coli, and Bacteroides [12]. In IBS-D patients there is an increase in the number of gas and fatty acids producing bacteria, also having a higher capacity of deconjugating bile acids [37].

Pimentel and his co-workers found out a surprisingly increased number of IBS patients (78%) to have a positive lactulose hydrogen breath test. A positive test is defined as a double peak in breath hydrogen, the first occurring less than 90 minutes after ingestion, with a rise of more than 20 parts per million [38]. This finding can be suggestive of the presence of small intestinal bacterial overgrowth (SIBO) providing the rationale for antibiotic treatment. In his studies [39,40] a 10 day course of broad spectrum antibiotics (neomycin, ciprofloxacin, metronidazole, or doxycycline) or rifaximin, improved the symptoms, including diarrhea in around 37 to 67% of cases.

The problem of small intestinal bacterial overgrowth in controversial. There are researchers who didn't find any difference in lactulose breath test between IBS patients and asymptomatic controls, only 4% of individuals having abnormal lactulose breath test. Other studies reported that only 30% of IBS patients had bacterial overgrowth, their number being slightly higher than in controls [12].

Recent studies sustained the efficacy of rifaximin in IBS patients with SIBO. SIBO was present in about 56% of IBS patients, and treatment with rifaximin in a dose of 1200 mg/day for 7 days significantly reduced the symptoms, especially in those patients with an alternated constipation/ diarrhea-variant IBS [41].

Probiotics are a more attractive way of altering bowel flora. Probiotics have a beneficial effect on intestinal mucosa via several proposed mechanisms that include suppression of the growth and binding of pathogenic bacteria, improvement of the barrier function of the epithelium, and alteration of the immune activity of the host. Probiotics decrease luminal pH and production of bactericidal proteins and may improve bowel dysmotility [42].

Probiotics are used with success in acute gastroenteritis, diarrhea secondary to antibiotic treatment, lactose intolerance, pouchitis after proctocolectomy, intestinal infection with Clostridium. They might play a role in treating IBS-D patients [12]. There are a lot of studies assessing probiotics in the treatment of patients with IBS, a lot of them showing benefit for some symptoms, notably bloating and flatulence, without a significant impact on diarrhea. These trials have typically included strains of *Lactobacillus* species (L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus, and L. plantarum), *Bifidobacterium* species (B. longum, B. infantis, and B. breve), and *Propionibacterium* species, along with different probiotic combinations such as VSL#3 and SCM-III. Many of the studies involved were small in size, of short duration, and had significant design flaws, but there is growing evidence that *B. infantis* is becoming the frontrunner for treatment of IBS [12,42]. A small study from 2009, on 52 patients with IBS-D concluded that Bacillus coagulans is a safe and effective probiotic for reducing daily bowel movements in patients with IBS-D [43].

2.7. Miscellaneous agents

There are reports that octreotide (20 mg im /day for 8 weeks) improved stool consistency compared with placebo (loose stools after eight weeks: octreotide: 52%, placebo: 81%). In contrast, abdominal pain and defecation frequency were not affected [44].

Some studies and a systematic review show that asimadoline (a kappa-opioid agonist), 0.5 mg twice a day for 12 weeks, improved abdominal pain, but in the same time urgency and stool frequency when compared with placebo. Also the drug was well tolerated. Asimadoline shows efficacy in the treatment of IBS-D [45,46].

3. Psychological treatment is based on the assumption that IBS symptoms are a response to stressful life events or daily hassles, producing maladaptive behaviour and inappropriate symptom attributions. Some of the techniques used so far are relaxation training, cognitive behavioural therapy, psychodynamic interpersonal therapy and hypnotherapy. Some of the best results are with hypnotherapy which improves all the symptoms, quality of life and psychological status. Furthermore, the beneficial effects appear to be sustained over time, with patients reporting continued relief from symptoms for at least five years [8].

Conclusion

Therapy of diarrhea in irritable bowel syndrome is sometimes a difficult problem. There are a lot of studies about therapy in IBS; usually some general scores are measured and not all the studies give specific results about stool frequency or consistency. The efficacy of these methods of treatment it's sometimes only slightly better than placebo. Currently, no therapeutical option is suitable and efficient for all IBS cases with diarrhea. Probably the best way is to start gradually, with the most simple drugs (i.e. antispasmodic) and probiotics, trying in the same time to reduce daily hassles. Loperamid, diosmectite and alosetrone may be efficient in severe cases.

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