Role of GI motor abnormalities in irritable bowel syndrome

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Introduction

There is still no category of gastrointestinal disease that fosters a greater sense of frustration in physicians and patients than functional gastrointestinal disorders. This frustration reflects the paucity of effective medications, and is only tempered for the physician by the knowledge the diagnosis is most often correct, and safe, that is, patients do not develop significant complications or die from these disorders. Regrettably, the patients experience impaired quality of life, and utilize health care resources extensively as they seek better "solutions" (including unnecessary repeated investigations or even surgery). From a societal standpoint, there is also a significant economic burden estimated for 1998 at $41 billion for the 8 most industrialized countries ; two thirds of this burden reflects absenteeism from work and the indirect costs.

During recent years, a greater understanding of the pathophysiology of these disorders and a surge of interest in this challenge among pharmacologists, basic scientists, and clinical investigators have led to novel insights and promising therapies.

Irritable bowel syndrome (IBS) is a disorder that can be diagnosed positively on the basis of a series of symptom criteria, and limited evaluation to exclude organic disease. It affects about 15% of all people at any one time. While only 10% of IBS patients seek medical care, the illness has an enormous economic impact through direct costs in healthcare utilization, and indirect costs through absenteeism from work. IBS is a biopsychosocial disorder resulting from a combination of 3 interacting mechanisms : psychosocial factors, altered motility and altered sensory function of the intestine.

Symptomatic treatment includes fiber for constipation, loperamide for diarrhea, and low dose antidepressants, hypnotherapy, psychotherapy or infrequent use of antispasmodics for pain ; several novel pharmacologic agents based on an ever increasing fund of knowledge regarding mechanisms and mediators of enteric motility and sensation augur well for improved therapy in the future.

We will review the motor abnormalities that have been found to be present in IBS, and we will briefly discuss some of the therapeutic approaches that are aimed at correcting motor disturbances in IBS. A role for motility disturbances in the occurrence of IBS is evidenced by the definition of IBS, by data obtained from physiological studies, and finally by responses to treatment aimed at correcting dysmotility.

Definition of IBS

Irritable bowel syndrome (IBS) is defined as "a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, with features of disordered defecation and distention." The consensus definition and criteria for IBS have been formalized in the "Rome criteria", which are based on Manning's criteria (Table I) (1). Manning's criteria have diagnostic value in the many patients with suspected IBS, particularly female patients (2) ; the Rome criteria have been widely used in clinical research (3). Validation of these criteria however, has been hampered by the lack of any biological marker for IBS. The Rome criteria have come to be accepted as the state-of-the-art criteria for research studies ; they have recently been refined and simplified for IBS to focus on the essential elements of abdominal pain and alteration of bowel habits (4).

The fact that a change in bowel habits is a fundamental characteristic in defining IBS, implies that IBS is also a disorder of motility.

Table I. — **Manning Criteria for IBS**

1. Pain relieved by defecation
2. More frequent stools at the onset to pain
3. Looser stools at the onset of pain
4. Visible abdominal distention
5. Passage of mucus
6. Sensation of incomplete evacuation

Data from Manning A.P., Thompson W.G., Heaton K.W., Morris A.F. Towards a positive diagnosis of the irritable bowel. *British Medical Journal*, 1978, **2** : 653-654.

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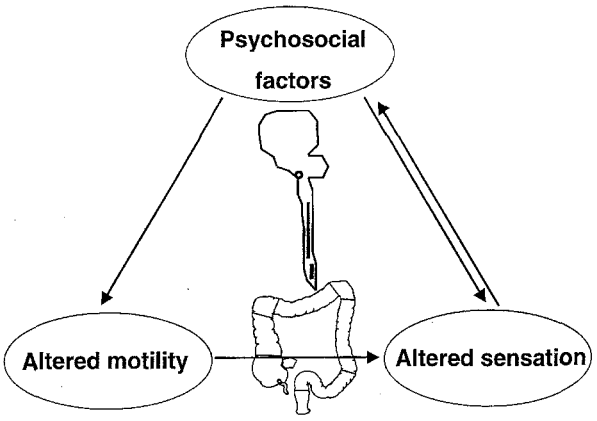

Fig. 1. — Conceptual framework for mechanisms interacting in the development of irritable bowel syndrome, a biopsychosocial disorder involving the brain-gut axis. Adapted with permission from Camilleri M., Choi M.-G. *et al. Aliment Pharm. Ther.*, 1997, **11** : 8-15.

Role of abnormal motor function in IBS

Symptoms in IBS have a physiological basis but there is no single physiological mechanism responsible for symptoms of IBS. Proposed pathophysiological mechanisms for IBS are summarized in table II. Some dysfunction may predominate, but it is conceivable that more than one operates in any individual (5). IBS is thus considered to be a biopsychosocial disorder in which both altered motility or sensation in the small bowel or colon are modulated by input from the central nervous system (6,7). A prior infectious gastroenteritis may be a precipitating factor in about a quarter of patients (8). Persistence of symptoms in these patients is at least partly related to psychological factors. It is hoped that identification and better understanding of the mechanisms of IBS will lead to the development of more effective therapeutic strategies.

Table II. — **Mechanisms in irritable bowel syndrome***

- Abnormal motility
- Abnormal visceral perception
- Psychologic distress
- Luminal factors irritating small bowel or colon
  - lactose, other sugars
  - bile acids, short-chain fatty acids
  - food allergens
- Post-infectious neuromodulation

* Interaction between different mechanisms.

Abnormal motor function in IBS patients

Based on data obtained from a multitude of studies, which addressed the role of abnormal GI motor patterns and functions in IBS patients, following intestinal and colonic motor alterations may operate in IBS (5,6) :

- Psychologic and physical stress increase colonic contractions (8-10) ;
- Patients with a clinically-prominent gastrocolonic reflex display increased postprandial distal colonic contractions (11) ;
- Abnormal motor patterns in the small bowel have been implicated in the generation of symptoms in IBS. Clustered contractions in the upper small intestine and ileal propagated giant contractions were observed during episodes of abdominal colic (12,13).
- Symptom subgroups of IBS based on bowel habit alterations, are reflected by motor abnormalities. Number of fast colonic and propagated contractions is increased with diarrhea (14, 15) and decreased in constipation-predominant IBS (16) ; patients with IBS and diarrhea have accelerated whole gut (17) and specifically ascending and transverse colon transit, which is positively correlated with stool weight (18). Patients with idiopathic constipation, normal colonic diameter and normal anorectal and pelvic floor function have overall delays in colonic transit (19).

Among constipation-predominant IBS patients with excessive straining or sense of incomplete evacuation, it is essential to exclude a rectal evacuation disorder (anismus, pelvic floor dyssynergia) for which re-training rather that pharmacotherapy is the treatment of choice.

Therapeutic approaches aimed at correcting dysmotility in IBS

Antidiarrheal agents in IBS

Diarrhea-predominant IBS is associated with acceleration of small bowel and proximal colonic transit (20,21). Loperamide (2-4 mg, up to 4 times daily), a synthetic opioid, decreases intestinal transit, enhances intestinal water and ion absorption, and increases anal sphincter tone at rest. These physiological actions explain the improvement in diarrhea, urgency, and fecal soiling observed in patients with IBS (22). The effect on resting anal tone (22-27) may help reduce fecal soiling, in particular at nighttime. Loperamide does not cross the blood-brain barrier and is therefore preferred over other opiates such as diphenoxylate, codeine, or other narcotics for treating patients with IBS who have predominant diarrhea and/or incontinence. Loperamide is also used to reduce postprandial urgency associated with a prominent colonic response to a meal or as a means of improving control at times of anticipated stress or other colonic stimuli (e.g., exercise, social gatherings, etc.).

Bile acid sequestration may relieve the choleric effect of bile acids in patients who have idiopathic bile acid malabsorption (28). Cholestyramine, however, is considered as a second-line treatment in IBS with predominant diarrhea. The rationale is based on the documentation of bile acid malabsorption in patients with functional diarrhea that mimics IBS with diarrhea (29,30). The simpler, often more acceptable approach in patients who find cholestyramine distasteful or in whom bile acid

Figure 2

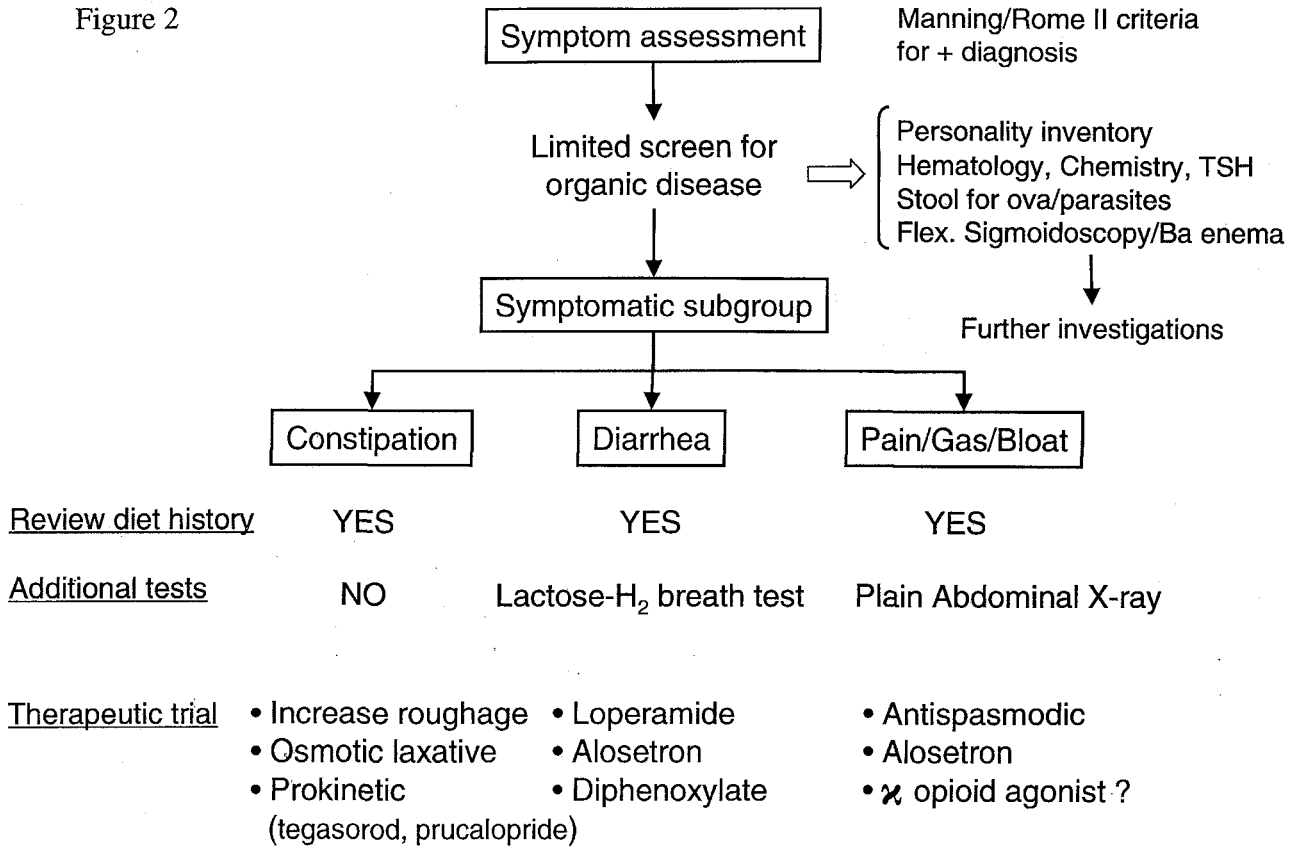

Fig. 2. — Management algorithm detailing a practical approach to the patient presenting with IBS. Reproduced with permission from Coulie B., Camilleri M. *Clin. Perspectives Gastroenterol.*, 1999, **2** : 329-338.

sequestrates are contra-indicated, is to use loperamide as a first measure for bile acid malabsorption.

New treatment options

Pharmaceutical companies have identified agents with visceral analgesic properties, and this has led to a surge in the development of novel drugs for IBS, such as the kappa opioid agonist fedotozine, $5HT_3$ and $5HT_4$ antagonists specifically aimed at restoring normal visceral sensation, and $5HT_4$ agonists with significant colonic prokinetic activity (Table III). Several of these novel approaches are in the process of thorough evaluation in phase II or phase III trials, such as the kappa opioid agonist fedotozine (31). Alosetron, a $5HT_3$ antagonist, is effective in relieving pain and normalizing bowel frequency and reducing urgency in non-constipated IBS female patients (32,33). The $5HT_4$ agonists tegasorod (34,35) and prucalopride (36) are currently in phase III trials for constipation-predominant IBS. Other research studies are currently exploring the potential of $alpha_2$ adrenergic agonists (clonidine) and $5HT_1$ agonists (buspirone) (37,38).

We will review alosetron (Lotronex) (39), a $5HT_3$ antagonist which appears to be very promising in the treatment of abdominal pain and discomfort and normalizing bowel function in patients with non-constipated IBS, and tegaserod (Zelmac) and prucalopride, $5HT_4$ agonists with potential for treating constipation-predominant IBS. The discussion of the latter drugs is more limited since they are somewhat behind alosetron in the drug development process.

Alosetron is a potent and selective antagonist at the $5\text{-}HT_3$ receptor, which mediates physiological functions in the gastrointestinal tract. $5\text{-}HT_3$ receptors are located on vagal and visceral afferents. Thus, antagonists operating either on vagal afferents or on central receptors in the chemoreceptor trigger zone and vomiting center in the base of the fourth ventricle result in a marked diminution in emesis following chemotherapy and radiotherapy.

In irritable bowel syndrome, hyperactivity of the motor response to meal ingestion, or hypersensitivity to luminal distention result in symptoms which originate in the small bowel and colon. Pharmacodynamic studies of an earlier $5\text{-}HT_3$ antagonist (ondansetron) demonstrated that the antagonist suppressed the reflex activation of colonic motor function in response to food ingestion in health (40) and disease states (41). The latter reflex is a prominent feature of normal postprandial function but, in certain disease states, it tends to be exaggerated. This manifests as urgency, abdominal cramping, and diarrhea

Table III. — **Novel IBS pharmacotherapy : based on pathophysiology and pharmacodynamics**

"Key" Targets : Sensation, tone and the "Gastrocolonic Response"
$Alpha_2$ agonists Clonidine reduces tone, increases compliance, decreases pain sensation during mechanical stimulation
Anticholinergics Selective M3 type
Calcium Channel Blockers Reduce rectosigmoid response to distension
CCK Antagonist Loxiglumide does not inhibit colonic response to food ingestion in humans
Kappa opioid agonist Peripheral opioid, pain-relieving agent
$5HT_1$ Agonist Relaxes colonic tone, reduces sensation
$5HT_3$ Antagonist Reduces gastrocolonic tonic response Reduces colonic compliance ? effect on afferents
$5HT_4$ Agonist Enhances colonic motility and transit
$5HT_4$ Antagonist ? inhibits colonic sensation
Neurokinin antagonists ($NK_{1,2,3}$) Inhibits colonic sensation
Somatostatin Analog Reduces visceral sensation Inhibits tonic response, increases phasic response to meal

in the early postprandial period in patients with diarrhea-predominant or alternating form of irritable bowel syndrome.

The effects of 5-HT_3 antagonists appear to be mediated predominantly by inhibiting visceral afferent responses that either result in direct pain activation or stimulate motor function of the colon.

The main indication for alosetron is irritable bowel syndrome in non-constipated female patients ; in these patients, alosetron results in adequate relief of pain, reduced urgency to defecate, increased stool consistency, and reduced frequency of bowel movements. The optimal dose is 1 mg b.i.d. It will probably be used as an adjunct to loperamide for those with urgency and uncontrollable diarrhea, or to control diarrhea and pain especially if loperamide causes rebound constipation, or when antispasmodics/antidepressants do not provide sufficient pain relief.

Tegaserod is an amino guanidine-indole with selective and partial $5HT_4$ receptor agonist activity (42,43). $5HT_4$ agonists possess gastrointestinal stimulatory effects, partially by facilitation of enteric cholinergic transmission (44).

In a Phase 2 trial in over 500 patients with constipation-predominant IBS, tegaserod improved subjective symptoms of IBS, increased stool frequency and decreased abdominal discomfort (45). The maximum effect was observed with 2 mg and 6 mg b.i.d. A recent study by Lefkowitz *et al.* (35) showed a significant improvement of abdominal discomfort or pain in 799 patients with constipation-predominant IBS. Symptomatic improvement was accompanied by normalization of the frequency of bowel movements. The main indications for tegaserod will probably be slow transit constipation and constipation-predominant IBS. The optimal dose will be between 2 mg and 6 mg b.i.d.

Prucalopride is a benzofuran 5-HT_4 receptor agonist that has been shown to facilitate colonic neurotransmission (46). It enhances colonic contractility, including giant migrating contractions, and accelerates the propulsion of stool in dogs (47).

In a recent study in 61 patients with functional constipation or constipation-predominant irritable bowel syndrome, we showed that prucalopride 2 mg and 4 mg daily accelerated overall gastric emptying and small bowel transit. Prucalopride tended to accelerate overall colonic transit with significantly faster overall colonic transit and ascending colon emptying with the 4 mg dose (48).

Several placebo-controlled trials of longer duration have investigated the effects of prucalopride on reported bowel movement frequency in patients with constipation (36,49,50). Each of these phase II trials, wherein prucalopride was given daily for 4 weeks, showed a dose-dependent increase in the number of bowel movements when prucalopride was compared to placebo. Taken together, these findings suggest prucalopride accelerates colonic transit and improves bowel habit. This agent may play a future role in the management of patients with functional constipation or constipation-predominant IBS. Ongoing phase III trials of prucalopride are being pursued for the long-term management of patients with constipation.

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