Motor function in irritable bowel syndrome

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M Camilleri. Motor function in irritable bowel syndrome. *Can J Gastroenterol* 1999;13(Suppl A):8A-11A. The evidence supporting a role of abnormal motor function in irritable bowel syndrome (IBS) is reviewed. Symptoms commonly present in IBS patients, such as vomiting, diarrhea, constipation or incomplete rectal evacuation, indicate that a motor disorder is implicit as either a primary or secondary disturbance. Physiological studies implicate a disturbance of transit through the small bowel and proximal colon, and abnormal motor responses of the rectum to distention in IBS patients. Intestinal contractions (physiological or 'abnormal') are associated with the sensation of pain, suggesting that these contractions are interactions between abnormal motor and sensory functions in IBS. Therapies aimed at correcting abnormal transit or antispasmodics are the main pharmacological approaches to the relief of IBS, and, although the latter are not always effective in the long term response to treatment, they support the role of dysmotility in IBS. Most novel therapies under trial probably modulate both sensory and motor functions, and are discussed briefly. In summary, the weight of clinical, physiological and pharmacological evidence supports a role of abnormal motility in IBS.

Key Words: *Constipation, Diarrhea, Irritable bowel syndrome, Motor function*

La motricité dans le syndrome du côlon irritable

RÉSUMÉ : On passe ici en revue les preuves du rôle de la dysmotilité dans le syndrome du côlon irritable (SCI). Les symptômes les plus souvent observés chez les patients atteints de SCI, comme les vomissements, la diarrhée, la constipation ou l'évacuation rectale incomplète, évoquent de façon implicite la dysmotilité comme anomalie primaire ou secondaire. Des études physiologiques mentionnent un transit anormal dans le grêle et le côlon proximal et des réactions motrices rectales anormales à la distension du rectum chez les patients atteints de SCI. Les contractions intestinales (physiologiques ou « anormales ») sont associées à la sensation douloureuse, ce qui donne à penser que ces contractions reposent sur des interactions perturbées entre les fonctions motrices et sensorielles. Les traitements visant à corriger le transit anormal ou les antispasmodiques sont les principales approches pharmacologiques pour le soulagement du SCI et bien que ces derniers ne soient pas toujours efficaces, par la réponse à long terme au traitement, ils tendent à confirmer le rôle de la dysmotilité dans le SCI. Les thérapeutiques plus récentes à l'essai agissent probablement sur les fonctions motrices et sensorielles et on les mentionne brièvement. En résumé, le poids des preuves cliniques, physiologiques et pharmacologiques confirment le rôle de la dysmotilité dans le SCI.

The most convincing evidence for the role of motility in irritable bowel syndrome (IBS) stems from the definition of IBS, results of physiological studies and the responses to treatments aimed at correcting dysmotility.

MOTOR DYSFUNCTION IS IMPLICIT IN THE DEFINITION OF IBS

According to the 'Rome criteria', 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" (1). The change in bowel habit implies that IBS is a disorder of motility.

An obvious deficiency in the Rome definition of IBS is the absence of symptoms such as urgency and abdominal pain, or diarrhea in the postprandial period, which also implies a motor disturbance. Several studies, including the classical one by Chaudhary and Truelove (2), have shown that a prominent gastrocolonic response to feeding is characteristic of a subgroup of patients, and that this response can be assessed subjectively and objectively with colonic manometry.

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Patients with functional diarrhea associated with postprandial urgency and borborygmi, and a sense of incomplete rectal evacuation are regarded by many clinicians as suffering from a variant of IBS, despite the absence of abdominal pain, and are not identified according to the Rome criteria.

WHAT MECHANISMS LEAD TO IBS? ROLE OF ABNORMAL MOTOR FUNCTION

IBS is a biopsychosocial disorder in which altered motility or sensation in the small bowel or colon is modulated by input from the central nervous system, including the higher centres (Figure 1). Table 1 summarizes the pathophysiological mechanisms that lead to or aggravate IBS. Importantly, these individual mechanisms are not mutually exclusive. Thus, although some dysfunction may predominate, more than one may be operating in any individual. Understanding these mechanisms and identifying which ones pertain to an individual patient provide a basis for optimizing the management of IBS.

The abnormal motor functions of the digestive tract in IBS have been recognized for several decades (3-6). More recently, markers of altered motor function have been described during small bowel motility studies in patients with IBS. Horowitz and Farrar (7) were the first to observe clustered contractions during episodes of abdominal colic. Kellow and Phillips (8) confirmed this finding and identified the coincidence of painful cramps with the passage of high amplitude pressure waves through the ileocecal region, suggesting that altered sensation is an important cofactor of the clustered activity. Gorard et al (9) showed no increased frequency of clusters in patients with IBS with diarrhea compared with healthy people. Patients with diarrhea-predominant IBS have more jejunal contractions during phase II and postprandially than healthy subjects. The colons of patients with diarrhea-predominant IBS have a greater number of fast contractions (10) and propagated contractions (11). Functional diarrhea is associated with normal colonic tone and increased postprandial high amplitude propagated contractions (12). In contrast, patients with constipation-predominant IBS have fewer high amplitude propagated contractions (13).

Cann and colleagues (14) showed that patients with IBS and diarrhea had accelerated whole gut transit times; in some patients, fast orocecal transit was also observed. Vassallo et al (15) showed that transit through the ascending and transverse colon is accelerated in patients with diarrhea-predominant IBS. This rapid transit through the proximal colon is positively correlated with stool weight (15). Conversely, patients with idiopathic constipation, normal colonic diameter, and normal anorectal and pelvic floor function have overall delays in colonic transit, with predominant slowing of proximal colonic emptying (16,17).

The increased sensitivity of the anorectum is accompanied by the development of excessive reflex motor activity in the rectum (18). These observations suggest that there are interactions between excessive sensation and motor responsiveness. Interestingly, increased rectal sensitivity is exclu-

Figure 1) Conceptual framework for mechanisms interacting in the development of irritable bowel syndrome, a biopsychosocial disorder involving the brain-gut axis. Reproduced with permission from reference 31

TABLE 1
Mechanisms in irritable bowel syndrome*

Abnormal motility
Abnormal visceral perception
Psychological distress
Luminal factors irritating the small bowel or colon
Lactose, other sugars
Bile acids, short chain fatty acids
Food allergens

*Interaction between different mechanisms

sive to patients with diarrhea- or urgency-predominant IBS (18,19). Thus, increased anorectal sensitivity may explain the symptoms of pain before bowel movements and a sense of incomplete evacuation, while the increased motor response to these stimuli may result in the increased frequency of bowel movements, often unassociated with increased stool weight in patients with IBS. The level of rectal compliance and tone also influences rectal sensitivity during mechanical stimulation (20).

LUMINAL FACTORS IRRITATING THE INTESTINE MAY ALTER ITS SECRETOMOTOR FUNCTION

There are several situations in which factors present in the intestinal lumen may alter intestinal function, causing an irritated gut (21). These luminal factors probably aggravate the underlying IBS rather than being an intrinsic component of the syndrome, and include exogenous dietary components and possibly endogenous chemicals involved in the digestive process. Malabsorbed sugars and food allergens may be important in IBS. Experimentally, luminal antigenic challenge in the sensitized rat intestine induces prominent contractile activity and diarrhea (22).

Figure 2) Algorithm detailing a practical approach to management of irritable bowel syndrome. Ba Barium; ELEC Electrolytes; ESR Erythrocyte sedimentation rate; Flex Flexible; O Ova; OSM Osmolality; P Parasites; SB Small bowel; TSH Thyroid-stimulating hormone; yr Year. Reproduced with permission from reference 31 and adapted from a similar algorithm in reference 27

The ileum of patients with IBS is excessively sensitive to the secretory effects of perfused bile acids (23). Bile acid malabsorption may be underdiagnosed (24). Short or medium chain fatty acids, which may reach the right colon in patients with borderline absorptive capacity or rapid transit in the small bowel, induce rapidly propagated, high pressure waves in the right colon. These waves propel colonic content extremely effectively and may result in pain or diarrhea (25,26).

INITIAL TREATMENT OF IBS

Figure 2 provides a management algorithm for IBS (27). If no specific dietary intolerance is identified, diarrhea in IBS patients should be treated symptomatically with anti-diarrheals such as diphenoxylate or loperamide (28). Tricyclic antidepressants, such as desipramine 50 mg tid or amitriptyline 10 to 25 mg bid, significantly relieve diarrhea and associated pain; these effects appear to be at least partly due to the anticholinergic actions of the tricyclic antidepressants (29). Calcium channel blockers (such as verapamil 40 mg bid) may be used as a secondary treatment (30). Constipation and osmotic agents, and moderate fibre supplementation are first-line measures, and laxatives or prokinetics are second-line measures.

THERAPY DIRECTED AT ABNORMAL MOTILITY IN IBS

Table 2 summarizes the literature on the effectiveness of smooth muscle relaxant medications (31). These data are based on results from published articles of randomized, double-blind, placebo controlled studies of at least two weeks' duration. The mean response for abdominal pain was 68% (range 23% to 87%) for active medication and 31% (range 22% to 66%) for placebo. Similarly, for global assessment, mean responses to drug and placebo were 73% (range 39% to 89%) and 41% (range 13% to 69%), respectively. A meta-analysis by Poynard et al (32) indicated that some of these agents, such as mebeverine, octylonium and cimetropium, are worthy of trial. Several novel approaches (Table 3) are also in the process of thorough evaluation in phase II or phase III trials, such as the kappa opioid agonist fedotozine,

TABLE 2
Efficacy of anticholinergics and antispasmodics in the treatment of irritable bowel syndrome

	Design	n	Duration (weeks)	Abdominal pain			Overall assessment			Side effects
				Drug	Placebo	P	Drug	Placebo	P	
Mebeverine	PG	40	16	23%	28%	NS				None
	XO	24	8	83%	33%	<0.05	83%	33%	<0.05	None
	XO	60	2	71%	22%	<0.001	71%	25%	<0.001	10%
	PG	36	8				81%	55%	<0.01	
Peppermint oil	XO	29	2				83%	17%	<0.001	
	XO	41	2				39%	52%	NS	24%
	XO	18	3				50%	13%	<0.01	
Octylonium	XO	60	2	73%	22%	<0.001	71%	25%	<0.001	10%
Prifinium	XO	18	3				78%	33%	<0.01	
Trimebutine	XO	20	4	60%	20%	<0.01				
	PG	30	24	75%	66%	NS	62%	68%	NS	
Cimetropium	PG	35	24				89%	69%	<0.05	
	PG	15	24	80%	28%	<0.05				
	PG	48	24	87%	16%	<0.01	87%	24%	<0.01	48%
Dicyclomine	PG	49	2	56%	41%	<0.05	84%	53%	<0.01	
Hyoscine	PG	182	4				76%	64%	<0.001	

PG Parallel group; XO Crossover

TABLE 3

Future irritable bowel syndrome pharmacotherapy based on pathophysiology (key targets are sensation and the gastrocolonic response)

Anticholinergics
Selective M3 type
Cholecystokinin antagonist
Loxiglumide does not inhibit gastrocolonic response
Somatostatin analogue
Reduces visceral sensation
Inhibits tonic response, increases phasic response to meal
5-Hydroxytryptamine ₃ antagonist
Reduces gastrocolonic tonic response
Possible effect on afferents
Calcium channel blockers
Reduce rectosigmoid response to distension
Others in development
Kappa opioid agonist
5-Hydroxytryptamine ₄ antagonist
Adrenergic agents (alpha ₂ agents)
Substance P antagonist

and 5-hydroxytryptamine₃ and 5-hydroxytryptamine₄ antagonists (33,34).

Alternative therapeutic strategies for patients with significant pain are hypnotherapy or psychotherapy, but their effects on motor function have not been explained.

CONCLUSIONS

Data from clinical observations, and physiological and pharmacological studies support the concept that abnormal motor function is an important primary or secondary component of IBS.

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