Irritable bowel syndrome: New approaches to its pharmacological management

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G Tougas. Irritable bowel syndrome: New approaches to its pharmacological management. Can J Gastroenterol 2001;15(Suppl B):12B-13B. The present paper examines approaches to drug therapy for irritable bowel syndrome (IBS). Because IBS is associated with multiple symptoms, no single therapy is effective in all patients. However, issues such as affective and emotional factors also need to be addressed when treating patients with IBS. This paper emphasizes the importance of identifying new pharmaceutical approaches to treat a multitude of symptoms and obtaining a better understanding of the underlying mechanisms of IBS.

Key Words: *Irritable bowel syndrome; Pharmacotherapy*

Syndrome du côlon irritable : nouvelles approches pharmacothérapeutiques

RÉSUMÉ : Le présent article traite des différentes approches pharmacothérapeutiques relatives au syndrome du côlon irritable. Comme ce dernier est associé à une foule de symptômes, il n'existe pas de traitement efficace universel. Par ailleurs, il faut tenir compte des facteurs émotifs et affectifs mis en cause dans le syndrome. L'article fait ressortir l'importance des nouvelles approches pharmacothérapeutiques pour soulager les nombreux symptômes et mieux comprendre les mécanismes sous-jacents du syndrome.

In recent years there has been a resurgence of interest in the pharmacological treatment of the symptoms associated with irritable bowel syndrome (IBS). This interest is in contrast with the very negative conclusions of Klein (1), who reviewed the available clinical trials related to drug therapy in IBS in 1988 and who had concluded, at that time, that there was no evidence that any of the therapies available were better than placebo. However, most physicians involved in the care of patients with IBS still use pharmacotherapy in some subsets of patients with IBS. In a recent document, the American Gastroenterological Association examined the possibility of practice guidelines in this area while acknowledging the relatively poor quality of the available evidence (2). If nothing else, the widespread acceptance of the Rome criteria as a diagnostic basis for patient selection in clinical trials for IBS has led to more rigorous drug treatment trials.

In parallel to the largely epidemiological concerns of the Rome meetings, others groups have markedly expanded the understanding of the basic mechanisms involved in the pathophysiology of IBS. This pathophysiological approach has, in turn, led to the development of several promising compounds that may prove to be useful in the management of certain subsets with functional gastrointestinal complaints.

At the outset of any discussion of the management of patients with IBS, it is important to remember that IBS defines an arbitrarily defined amalgam of symptoms that include abdominal pain (or discomfort), and various alterations of stool and defecation. This amalgam is very different from an actual disease entity with recognized pathogenic mechanisms. In fact, several mechanisms and pathological processes may contribute to the generation of the heterogeneous symptoms that constitute IBS. The Rome criteria may be of some use at the epidemiological level, they are of little use in the development of novel therapies and in the context of therapeutic development, and should be abandoned in favour of a more pathophysiological approach. To be effective, drug therapy should target the mechanisms likely responsible for the symptoms. Because patients with IBS exhibit multiple symptoms that are often the opposite extreme of a continuum (eg, constipation and diarrhea), no single therapy will ever be effective in all patients with these kinds of symptoms.

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Altered visceral perception (hypersensitivity to 5-hydroxytryptamine [5-HT]$_3$), altered function of the gut including motility and secretion, and the frequent presence of affective and emotional factors appear to be important dimensions in the majority of patients. The gut and brain are involved in the generation of the symptoms of IBS, as are the interactions between the two (gut-brain as well as brain-gut communication). These factors variably contribute to the generation of symptoms in different patients, but must be taken into account in the design of new therapeutic approaches.

VISCERAL PERCEPTION AND GUT-BRAIN COMMUNICATION

Both 5-HT$_3$ receptor antagonists and 5-HT$_4$ receptor agonists have been reported to alter visceral sensation and increase perception threshold during colonic distention. While several compounds have been examined, only the 5-HT$_3$ antagonist alosetron and the 5-HT$_4$ agonist tegaserod have been subjected to large placebo-controlled trials that have been published (3-5). However, these compounds also have definite pro- and antikinetic properties, and although these effects on visceral perception may be due to a direct action on visceral afferent pathways, they may also be indirectly due to a modulation of gut function and motor activity. Kappa opioid agonists such as fedotozine also have been recently found to be of some benefit in some patients with IBS-like symptoms (6,7). However, the effect was somewhat modest and development of these compounds subsequently terminated. *N*-methyl-D-aspartate and neurokinin (NK)$_1$ receptor antagonists are also being investigated for their visceral antinociceptive effects, but only preliminary results are available and await confirmation.

GASTROINTESTINAL MOTILITY AND FUNCTION

5-HT$_4$ agonists such as tegaserod have potent prokinetic actions throughout the gut in addition to their possible antinociceptive properties (8). Tegaserod has been found to be effective in chronic constipation and in patients with constipation-prone IBS, in short term and long term studies (9). Mixed 5-HT$_3$ antagonists and 5-HT$_4$ agonists are also being studied in similar populations, as are substance P agonists.

5-HT$_3$ antagonists such as alosetron and cilansetron have important hypokinetic colonic actions in diarrhea-prone IBS (3,4). In fact, it appears that most of the benefit derived from these drugs in IBS patients stems from this antidiarrheal action rather than from its modest antinociceptive effect (10). Muscarinic antagonists such as zamifenacin and NK$_1$ receptor antagonists also appear to have similar actions.

AFFECTIVE RESPONSE AND EMOTION

Several compounds including tricyclic antidepressants and serotonin-selective reuptake inhibitors (SSRIs) are presently being investigated in various subsets of patients with IBS (11,12). The former seem to be more effective in diarrhea-prone IBS patients (likely due to its anticholinergic action), whereas SSRIs may be better suited to constipation-prone patients (13). How applicable these drugs will be in less severe cases of IBS is questionable. Nonpharmacological techniques such as hypnosis, cognitive behavioural therapy, relaxation and stress management are also being investigated.

CONCLUSIONS

By using a symptom-based approach and through a better understanding of the mechanisms underlying these symptoms, several new compounds are being considered for the treatment of various subgroups of patients with IBS. Among these compounds, the most promising are those acting as 5-HT$_3$ receptor antagonists (alosetron) or as 5-HT$_4$ receptor agonists (tegaserod). Because these compounds appear to have antinociceptive and direct prokinetic or antikinetic properties on the gut neuromuscular function, they offer the promise of relief in broad subsets of patients with functional bowel symptoms.

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