Therapeutic strategy in irritable bowel syndrome

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Introduction

Functional gastrointestinal disorders are among the most frequent problems encountered not only in specialised gastroenterology consultations, but also in general medical practice (1,2). Irritable bowel syndrome (IBS) is a major component of this group of disorders. This syndrome was first clearly identified and defined by Manning (Table I) (3). Using his criteria a positive diagnosis can be proposed in the absence of an organic disease. More recently working parties on functional gastrointestinal disorders have developed new definitions and criteria. These are synthesised in the recently published Rome II criteria (4).

Various epidemiological studies have shown a high prevalence of IBS-symptoms in western countries ranging from 6.6 to 21.8%, with a majority of women. The heterogeneity of these results might not only be related to geographical variations in prevalence, but may also be due to the use of various diagnostic criteria (5). The recently published Rome II criteria seem to be more restrictive (6). On the other hand, not all patients with IBS-like symptoms seek medical care and are positively diagnosed with the syndrome. IBS patients have been shown to be more expensive in terms of health care when compared to a non IBS population. Different studies have shown that IBS has an important impact on the quality of life in a range similar to patients with inflammatory bowel disease. These findings highlight the impressive societal burden of this syndrome on wellbeing, health care costs and on loss of economical activity.

The progress in the understanding of the function of the enteric nervous system and its relations with the central nervous system (the so-called brain-gut axis), and the development of new investigational tools such as the barostat and functional imaging of the brain, have led to newer insights in the pathophysiology of this disease. There is now compelling evidence that IBS must be analyzed in view of a triangular interaction between motor and sensory disturbances of the gut and psychosocial factors. Each of these components have been dealt with elsewhere in this issue of this journal. The better comprehension of the pathophysiology of IBS has opened a new era of development of pharmacological compounds targeted on disturbed physiology.

Table I. — **Manning Criteria for diagnosis of Irritable Bowel syndrome** (3)

- Visible abdominal distension
- Relief of pain with bowel movement
- More frequent bowel movements with the onset of pain
- Loose stool at onset of pain
- Passage of mucus per rectum
- Feeling of incomplete evacuation

Current therapeutic management

Management of patients with IBS is a difficult task for a busy physician. Since IBS is a biopsychosocial disorder, both physiological and psychological interventions must be carried out. It is generally accepted that the first step is to build up a strong and confident therapeutic relationship with the patient. This statement is supported not only by the impressive placebo responses observed in most trials but also by data that such an attitude might reduce per se the number of health care visits (7). An important component of the therapeutic relationship is education and reassurance. It is of outmost importance to teach the patient that his symptoms are real and well understood, are recognized and will be taken care of. It is often helpful, if possible, to explain the three pathophysiological components of the syndrome and the interrelations between brain and gut. Such a clear approach is not only useful for educational purposes, i.e. to make clear to the patient that his problem is understood, but may also be used to explain the rationale for the use of pharmacological or non-pharmacological treatments. The use of a symptom diary for a limited period of time, may also be useful to enhance the patient's feeling of being understood. Reassurance needs a thorough identification of the apparent and hidden fears of the patient. In some cases a close collaboration with a psychologist or psychiatrist may be necessary in this respect.

Like any other functional gastrointestinal disorder, IBS is characterised by a fluctuating natural history. Over time subjects may alternate symptom-free periods, over moderately symptomatic periods, to periods with more pronounced symptoms which lead to consultation (8). Any psycho-social or environmental event may

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precipitate the passage from one category to another. The fluctuating course of the severity and nature of the symptoms is one of the main problems to perform qualitatively sound trials. Indeed, as most patients seek health care when their symptoms are most pronounced, the natural evolution, even without treatment is most likely to be favourable.

Strategy

Some researchers have proposed to stratify patients by severity in order to determine the therapeutic strategy (9). The different factors used to stratify patients are represented in table II. In addition, the same group of investigators designed a functional bowel disorder severity index to help classifying patients by severity (10). It is not clear however, if this strategy is preferable and/or very different to a stepwise approach in all patients. For example, in recent guidelines established by experts of the American Gastroenterological Association it is suggested to perform only a limited initial diagnostic work-up based on symptom subtype and initiate a baseline treatment (11). Only if at reassessment 3 to 6 weeks later symptoms persist, should further evaluation and more specific treatment be undertaken. We believe this stepwise approach is closer to the clinical practice and should be recommended.

In the following paragraphs we will present and discuss the current therapeutic interventions which can be proposed : lifestyle modifications, conventional pharmacological therapy, psychological treatment and antidepressant therapy.

Table II. — **Spectrum of clinical features among patients with IBS** (9)

Clinical features	Mild	Moderate	Severe
Estimated prevalence	70%	25%	5%
Practice type	Primary	Specialty	Referral
Correlation with gut Physiology	+++	++	+
Symptoms constant	0	+	+++
Psychosocial difficulties	0	+	+++
Health care use	+	++	+++

0 = Generally absent ; + = Mild ; ++ = Moderate ; +++ = Marked.

Lifestyle modifications

Diet

Most of the patients will attribute their symptoms to intake of specific food and will ask for dietary recommendations. Compelling evidence, however, is lacking to support the use of uniform dietary guidelines in IBS patients. Therefore, although it might be useful to recommend to avoid some substances, which in the patient's experience were associated to symptoms, such as excessively fatty foods, gas producing foods or coffee, care should be taken not to recommend useless restrictive diets. Dietary history should record the use of some sugar substitutes like sorbitol, which might exacerbate symptoms of IBS (12).

Fibres

Fibre supplementation has often been recommended as a first line dietary recommendation. There is however no proof of its efficacy on pain, which is the main symptom of IBS. In an open study, supplementation with an adequate daily dose of 20-30 g was compared to a placebo group of a drug trial. This study showed improvement of constipation, but no effect on abdominal pain when compared to placebo (13). Two randomized cross over trials with 13 g of bran supplementation or 20 g of corn fibre respectively did not show additional benefit of fibres over placebo in terms of symptomatic improvement (14,15). In the long term, fibre supplementation had equivocal benefit in a group of 14 patients with IBS followed for 2 to 3 years (16). It has even been suggested that fibre had a detrimental effect (17). All patients should therefore be warned that fibre supplementation might enhance some or all of their symptoms. This treatment should obviously only be recommended in constipated IBS patients.

Conventional pharmacological treatment

If reassurance, education and lifestyle modifications did not improve the patient's condition, one should consider the use of a pharmacological treatment. The efficacy of any pharmacological treatment in IBS has been critically reviewed in a landmark paper in 1988 (18). In this critique of available studies, Klein concluded there was no single agent which showed convincing evidence of proven efficacy. Since then however, the methodology of the clinical trials has been more accurate. A systematic review of available controlled trials has recently been published (19).

Since the aetiology of IBS has not been identified, no curative treatment can be proposed. Current pharmacological treatment is thus aimed at alleviating the symptomatic burden of the syndrome. There is a consensus in the literature that pharmacotherapy should be targeted at specific symptoms : abdominal pain, constipation and diarrhoea.

Abdominal pain and bloating

Abdominal pain and bloating are the key symptoms in IBS. Although the most frequently used compounds are antispasmodics, the evidence to support their use is not very strong. In an often cited meta-analysis, Poynard has shown that taken together the smooth muscle relaxants seem to improve abdominal pain and the global wellbeing (20). According to this analysis five drugs showed superiority to placebo : cimetropium bromide, pimaverium bromide, octylonium bromide, trimebutine and mebeverine. Even though the studies included in this meta-analysis were selected on methodological qualities, the huge variability of inclusion criteria, therapeutic endpoints and placebo response rates (5-80%) lead us to be cautious in interpreting the data and

recommending use of these medications. In addition, there is no data available whether to use this medication on a continuous or intermittent basis.

Constipation

Constipation is a significant component of the impaired quality of life in IBS patients. The potential role of dietary fibre supplementation in IBS has been discussed above. Although fibres probably have no role in the management of pain, they are frequently recommended for patients with constipation-predominant IBS. There are however, theoretical arguments against the use of fibres in IBS : bacterial fermentation of intra-colonic fibre may lead to distension of an already hypersensitive colon (21). In clinical practice it can thus be proposed to increase roughage and/or add fibre supplements in patients with constipation-predominant IBS, being aware that this intervention might increase the pain and bloating component of the syndrome.

The use of laxatives in constipation-predominant IBS is not widely recommended but might be helpful. Osmotic laxatives might be used safely. The use of lactulose may be hampered by the common side effect of bloating. On the other hand, given the chronic nature of the disorder and the presence of pain as a cornerstone symptom, it does not seem wise to use irritant laxatives.

An alternative way of treating constipation in IBS is by using a prokinetic. Several studies assessed the efficacy of cisapride in patients with irritable bowel syndrome (22,23,24,25). In the study by Schutze, constipation and abdominal discomfort were not improved. Only stool passage was eased in these patients during cisapride treatment. In the study by Noor which did not specifically select patients with constipation, constipation scores improved, whereas pain increased during the treatment. Only the study by Van Outryve showed efficacy on abdominal pain. Taken together, these data are discrepant and are not clearly in favour of the use of cisapride for constipation in patients with IBS.

Diarrhoea

Several trials assessed anti-diarrhoeals in IBS (26,27, 28,29). Consistently, loperamide showed advantage over placebo in the control of stool frequency, consistency and incidence of urgency. As expected, this compound had no effect on abdominal pain. Loperamide is preferred over diphenoxylate or codeine because it does not pass the blood-brain barrier. In cases where loperamide is not helpful, cholestyramine may be tried. The potential role of this drug is to sequestrate bile acids which have been absorbed in the ileum. The causal role of bile acid malabsorption in the diarrhoe-predominant IBS is however not well established and might be secondary to enhanced small bowel transit.

Psychological treatment

Since IBS cannot be considered as a purely gastrointestinal disorder, it seems logical to evaluate the role of psychological treatments in this condition. Several randomized controlled trials using various methods, such as hypnotherapy (30) and cognitive behavioural therapy with relaxation (31), have been published. These data suggest these therapeutic interventions might be useful. More details about these trials can be found elsewhere in this issue (32).

Antidepressant therapy

The interest in the use of antidepressants for patients with IBS was initiated on the frequent report of significant depression by those patients (33). The stigmatisation of IBS patients being prescribed antidepressant therapy has led to poor compliance and failure to gain acceptance. It is now recognized however, that the antidepressants have neuromodulatory and analgesic properties, independent of their psychotropic effect (34). In addition, these drugs might have a direct effect on the enteric nervous system thereby influencing both the motor and sensory pathways of gut neurophysiology. These effects might even become apparent at lower dosage regimens than those used for depression. This class of medication is therefore now widely used for the treatment of severe or refractory IBS. The most commonly used antidepressants are desipramine 50 mg tid (35) and amitriptyline 10-25 mg bid (36). Unfortunately, the scientific evidence supporting their use is not very well established, due to the poor quality of the available trials (19). Interestingly, the link between efficacy and psychological status was evaluated in three trials (37,35,36). Unfortunately, the results of this analysis were conflicting. It seems however that the presence of psychiatric disturbances is not required to obtain efficacy. In one study (35), IBS symptoms improved without concomitant improvement of depression. There are no controlled studies available with the use of newer antidepressant therapies in IBS such as selective serotonin reuptake inhibitors (SSRI). There are three arguments suggesting their usefulness. First these drugs have a more favourable toxicological profile. Second these drugs seems efficacious in other chronic painful conditions (38). Third there are some experimental arguments that one of these drugs (citalopram) decreases colonic sensitivity to distension and colonic tone (39).

Novel medications

The new pathophysiological insights of IBS have been dealt with elsewhere in this journal. This increasing understanding has revealed potential drug targets. The central role of serotonin (5-hydroxytryptamine or 5-HT) in sensory and motor physiology within the enteric nervous system naturally gave rise to the development of agonists and antagonists of its different receptors. The mixed sensitive and motor effects of these drugs due to their selective (in)activation of receptor subtypes will

give them specific clinical indications tailored to the symptomatic profile of the patients. In addition to serotonin, the newer targets are the κ-opioid receptor and the α_2-adrenergic receptors.

Alosetron

This 5-HT_3 antagonist has been developped to decrease visceral hypersensitivity. Indeed, 5-HT_3 receptors have been demonstrated on visceral afferent neurons. The activation of these receptors seems important in visceral sensation. Therefore, blocking these receptors leads to decreased visceral perception (40). Large phase III trials have already been performed both in North America and in Europe and have found global improvement and decreased abdominal pain, diarrhoea and urgency in diarrhoea-predominant female IBS patients with alosetron 1 mg bid (41). It is still not clear why only female patients did benefit from this treatment and this point is still under investigation. Unfortunately, 5-HT_3 receptors also play a role in motor and secretory function. This has lead to development of significant constipation in many patients (30% vs 3% on placebo) which can be treated either with osmotic laxatives or the insertion of a so called drug holiday. Finally, during these trials, some patients developed ischemic colitis for unclear reasons.

The study of other 5-HT_3 antagonist in IBS ongoing.

Fedotozine

This drug is an agonist at the κ-opioid receptor. This receptor mediates pain originating from the gut. In experimental studies it was shown that fedotozine given intravenously significantly reduced perception thresholds during barostatically controlled balloon distensions of the colon (42). A large scale clinical trial with fedotozine 30 mg tid during 6 weeks showed improvement of abdominal pain and bloating, without significantly affecting transit (43). Surprisingly, these very favourable initial results have not been followed by other studies and this drug is still not commercialised.

Octreotide

This somatostatin analogue has been shown to significantly increase the threshold for visceral perception as measured by barostat studies in patients with IBS. In these patients after medication both thresholds for discomfort and pain occurred at higher distension levels (44). Due to its various other physiological effects and to its parenteral administration, this drug was not further evaluated in this indication.

Clonidine

This drug was developed as a medication for arterial hypertension. Through activation of α_2-adrenergic receptors this medication interacts both with motor and sensory functions of the gut. In experimental setting, it reduces colonic tone and enhances pain thresholds during distension studies (45). So far this drug has not been evaluated for IBS in clinical trials.

Tegaserod

Tegaserod is a partial 5-HT_4 receptor agonist with promotile activity throughout the gut (46). Activation of 5-HT_4 receptors facilitates cholinergic transmission thereby enhancing smooth muscle contraction. Three phase-III trials in constipation predominant IBS have been performed and showed improved global discomfort scores and stool frequency (47). In view of its efficacy, not only on constipation but also on abdominal pain, this drug seems promising especially in Europe where clinicians feel constipation predominant IBS is more frequent than diarrhoea predominant IBS.

Prucalopride

Prucalopride is also a 5-HT_4 receptor agonist which has been shown to enhance colonic motility by induction of high amplitude propagated contractions in dogs and in humans (48). This prokinetic effect is not limited to the colon, but is also observed in the upper digestive tract (49). This promising drug has been extensively investigated in constipation, but was not yet assessed in patients with IBS with regard to pain or discomfort (50).

Conclusion

In this article we reviewed the current and future therapeutic approach of IBS. In view of the very high prevalence of the syndrome, of the variable presentation and of the changing symptom complex, a tailored stepwise therapeutic approach is recommended. First, a confident relation between patient and physician should be established. After failure of the initial non pharmacological approaches, medication should be prescribed based on the symptomatic pattern of the patient. Unfortunately, very few of the existing medications have an unquestionable efficacy, limiting possible pharmacological interventions. The expanding armamentarium, based on the increasing pathophysiological insight, however should allow physicians to treat each of the individual symptoms, thus improving the quality of life in these patients.

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