New approaches in the management and treatment of irritable bowel syndrome

Professor Robin Spiller
Division of Gastroenterology
University Hospital
Nottingham
NG7 2UH

Tel 0115 9709352
Fax 0115 9422232
E-mail robin.spiller@nottingham.ac.uk

The last few years have seen some important advances in our understanding of the irritable bowel syndrome (IBS). The new Rome II Criteria are simpler than Rome I (see Fig 1), and have undoubtedly improved the comparability of clinical trial populations though care is needed to avoid these criteria acting as blinkers and inhibiting progress in understanding pathogenesis.

Epidemiological studies suggest that symptom clusters define three sub-types of IBS. 1: characterised by loose stools passed with urgency with minimal straining, one characterised by hard stools and straining and incomplete evacuation but also some urgency and notably a similar bowel frequency. Finally there is a group of patients with minimal disturbance of stools and a normal stool frequency whose main complaint is pain and bloating. It is apparent therefore that stool frequency is an unreliable guide to sub typing since it depends on social and psychological factors. It is probably more useful to define IBS subtypes based on the stool consistency, which is closely related to colonic transit

Sub-typing IBS patients is important since lumping them altogether may miss beneficial effects if the treatment help one group but hinder another. Thus Loperamide improves patients with diarrhoea but worsens symptoms in those with constipation.

All clinicians are well aware that patients with a considerable psychological burden respond poorly to treatments. This was clearly shown by Bennett and colleagues who showed that those suffering from life stresses of greater than six months duration were less likely to improve than those who lacked such features.

When seeing a patient for the first time it is important to try and fit them into the multi-dimensional symptom space whose major axes are anxiety, colonic transit times and underlying pathology (Figure 2). The third dimension is poorly defined, apart from post infectious IBS (PI-IBS). These dimensions have important prognostic significance as can be seen in Fig 3. PI-IBS is characterised by abdominal cramps, lose and urgent stools and accounts for between 6 and 17% of IBS patients attending GI clinics. Physiological changes which affect nearly all individuals following GI infections include shortening of whole gut transit and lowering of discomfort threshold for rectal distension, the severity of the abnormality being increased in those who meet the criteria for IBS. Associated
with these changes there is also evidence of low grade inflammation and elevated
enteroendocrine cells which resolves in most patients, but persists in those with persistent
symptoms. These cells which are responsive to both luminal and neural signals are found
throughout the GI tract. More than 50% of these cells contain 5HT, in the upper gut CCK
and in the lower gut PYY account for most of the remainder. 5HT is released in response
to pressure, luminal nutrients and bacterial toxins including cholera toxins. It acts on a
range of receptors the most important of which in the GI tract are 1a, 1p, 2, 3 and 4.
Currently the most important ones therapeutically are 3 and 4. 5HT3 receptor is found
only on nerves and produces a short duration depolarisation, stimulating sensory nerves
including the vagus, thereby indirectly stimulating gastric and pancreatic secretions. It
also activates enteric cholinergic and VIPergic nerves, which stimulate enterocyte
secretion. 5HT4 receptors are found on both nerves and enterocytes. The receptor is G
protein-linked and when stimulated elevates cyclic AMP. This produces a slower onset
of action, inhibiting the delayed rectifier potassium channel and producing a prolonged
increase in the excitability of nerves, stimulating peristalsis and enterocyte chloride
secretion.

Peristalsis involves the action of a bolus distending the lumen exciting descending
inhibition and ascending contraction of the circular muscles. It is believed that the bolus
activates the enteroendocrine cells to release 5HT, which stimulates peristalsis (see
Figure 4). Enteroendocrine cell numbers have been reported as increased in patients with
chronic IBS seen in GI outpatients and a pilot study has reported an increased release of
5HT after a meal in diarrhoea predominant IBS. Postprandially 5HT appears to
stimulate both colonic tone and motility, effects which can be blocked by the intravenous
5HT3 antagonist, granisetron. Alosetron is a more specific 5HT3 antagonist which has
been shown to improve stool consistency in diarrhoea-predominant IBS and increase the
portion of patients experiencing adequate relief of symptoms. Its rather premature
withdrawal was unfortunately due to rare adverse events which were both expected
(severe constipation 70 / 435,000, 3 deaths) and unexpected (ischaemic colitis
40/435,000, no deaths). Tegaserod is a highly selective 5HT4 agonist which accelerates
GI transit and accelerates gastric emptying and small bowel transit and increases the
proportion of patients with relief of symptoms. It also increases stool frequency within
the first week. Both Alosetron and Tegaserod represent exiting new opportunities for
treatment in a field where there have been no new drugs for many years. However, we
should not become too over enthusiastic based on novelty alone. When assessing
efficacy it should be remembered that one needs to treat 8 – 9 patients with Alosetron or
Tegaserod to get one extra patient responding compared with placebo alone. The
challenge in the future is to better identify who will respond best to these treatments thus
improving the efficacy.

In summary, there are no panaceas! Individual patients require individual treatments. We
should always remember that as yet only psychological and dietary measures have been
shown to provide long-term improvement of symptoms. Not withstanding that drugs,
which have reliable benefit, may well be useful in providing a sense of control over these
symptoms which these patients so often lack.
Reference List


