IBS and SSRIs

How do SSRIs help patients with irritable bowel syndrome?

F Creed

Selective serotonin reuptake inhibitor antidepressants seem to promote global well being in some patients with irritable bowel syndrome and, possibly, some improvement in abdominal pain and bowel symptoms, but this effect appears to be independent of improved depression

In the randomised controlled trial reported in this issue of *Gut*, Tack and colleagues[1] compared citalopram and placebo in 23 patients with irritable bowel syndrome (IBS) over a six week initial treatment period using a parallel group design ***(see page 1095)***. The dose of citalopram was similar to that used in the treatment of depressive disorders but any patients with depressive disorder were excluded from this trial. The results showed that citalopram was superior to placebo in terms of the primary outcome measure—days with abdominal pain—and this improvement was unrelated to change in mood, change in stool pattern, or the effect of intravenous citalopram on rectal distension thresholds.

Overall this was not a good trial. The total number of outcome measures exceeded the number of subjects in the trial. The crossover part of the trial was discounted because symptoms did not return to baseline values after the first treatment period. It is not at all clear how the patients were selected and, therefore, whether the results might be generalised to clinic populations. Strengths of the study however include the high participation rate throughout the trial and the combined diary and questionnaire measurements.

In spite of the weaknesses of the trial design, this report is interesting because of the paucity of randomised placebo controlled trials of selective serotonin reuptake inhibitor (SSRI) antidepressants in IBS.[2 3] In one trial of patients who had failed to respond to a high fibre diet, Tabas *et al* found that a low dose of paroxetine was superior to placebo in terms of overall well being, IBS related anxiety, desire to continue the medication after the trial ended (before being unblinded), and less food avoidance.[4] The improvement in global well being was found even among non-depressed patients.

The other study by Kuiken *et al* found that in 40 non-depressed IBS patients, fluoxetine did not significantly alter the threshold for discomfort relative to placebo, either in hypersensitive or in normosensitive patients. In hypersensitive patients only, fluoxetine significantly reduced abdominal pain complaints without alteration of gastrointestinal symptoms, global symptom relief, or psychological symptoms.[5]

The trial by Tack and colleagues[1] does provide useful information if we examine only the a priori primary and two of the stated secondary outcome measures at the end of the initial parallel group comparison—that is, before the crossover part of the trial. These results show that citalopram was significantly superior to placebo in reduction of days with abdominal pain and days in which IBS impacted on daily life. Depression also improved significantly in the citalopram group compared with the placebo group but the improvement in IBS symptoms was not associated with improved mood.

Taken together with the previous results it appears that the SSRI antidepressants do promote global well being in some patients with IBS and, possibly, some improvement in abdominal pain and bowel symptoms, but this effect appears to be independent of improved depression. There are several possible mechanisms which might explain the beneficial effect of citalopram. All are independent of a change in mood and therefore might be applicable to the Tack study.

Firstly, the rationale of the present trial was based on a previous finding that intravenous citalopram decreased the sensitivity of the colon to distension in healthy volunteers.[6] In the trial, the result of intravenous citalopram did not predict outcome, but as no patients returned for further rectal distension testing after treatment it is not clear whether oral citalopram over six weeks led to a change in colonic sensorimotor function. As mentioned above, Kuiken and colleagues[5] found no such change so this seems to be an unlikely mechanism for the symptomatic improvement; only venlafaxine, which inhibits reuptake of both serotonin and norepinephrine, appears to decrease the sensitivity of the colon to distension.[7]

Secondly, citalopram, in common with other SSRI antidepressants, may have other effects on the gut, such as accelerating transit time,[8] which would help patients with constipation, but there was no clear evidence of this mechanism in this trial. Thirdly, there is some evidence that SSRIs have an analgesic effect. This is not as strong as tricyclic antidepressants when used for IBS,[3] neuropathic pain,[9] back pain,[10] or migraine[11] but appears to be important in patients with somatoform pain disorders.[12]

Probably more important than any of these possible effects on the gut is the effect on widespread bodily symptoms; citalopram may reduce the reporting of multiple bodily symptoms or ''somatisation''.[13] This may be the reason that SSRI antidepressants are beneficial in somatoform pain disorders,[12] premenstrual syndrome,[14] and for a variety of unexplained symptoms and syndromes.[15] These disorders are frequently concurrent with IBS but the nature of some of the IBS symptoms, which improved in the Tabas trial,[4] might fall into this category—overall well being, IBS related anxiety, desire to continue the medication after the trial ended, and less food avoidance. These symptoms may not be specifically related to gut dysfunction and may be part of the somatisation or ''extraintestinal'' symptoms that may accompany IBS.

In the present state of knowledge it is not clear how somatisation should be conceptualised in relation to IBS. Although IBS patients as a whole have high scores on somatisation measures,[16] it is likely that a subgroup of IBS patients is responsible for this finding; some IBS patients do not have an excess of bodily symptoms.[17 18] The presence of multiple bodily symptoms is associated with frequent treatment seeking[17 19] and this group of patients may need to be studied separated in future if we are to make sense of the role of SSRI antidepressants in IBS. Two groups which are known to report numerous bodily symptoms are those with a concurrent psychiatric disorder and/or a history of sexual abuse.

Patients with severe IBS who reported a history of sexual abuse seem to do particularly well following treatment with either paroxetine or psychotherapy, and the improvement in their health related quality of life is mediated by a reduction in somatisation.[20 21] Within this group of patients, who reported

abuse, the number of bodily symptoms was associated with rectal distension threshold, and an abuse history also predicted normalising of the distension threshold following treatment, independent of change in mood.[22] This change in rectal distension tolerance and reduced somatisation were probably related to a change in how bodily sensations were perceived; with treatment, the patients probably paid less attention to gastrointestinal sensations and ceased to attribute such sensations to possible serious disease.[23]

These psychological processes may be important in the last mechanism by which citalopram may lead to improved IBS symptoms. Citalopram has been shown to induce an affective memory bias towards positive material without significantly influencing the subjective mood status.[24] Citalopram ameliorates negative biases in information processing and this could reduce attention to gastrointestinal sensations and modify unrealistic fears that symptoms imply serious illness.

If reduction of somatisation and modification of memory bias towards more positive material underlie the action of citalopram in patients with IBS, is this important in the aetiology of IBS? The answer to this question is not clear. The psychological processes are certainly important in some patients but not all. It is likely that they are particularly important in relation to treatment seeking, which is driven, at least in part, by multiple bodily symptoms and fears of serious illness.

From a scientific point of view there are a number of weaknesses of the current and previous studies assessing efficacy of SSRI antidepressants, most notably their short duration and small sample sizes.[15 25] The latter is particularly important in relation to assessing whether different processes occur in different groups of IBS patients. Further large efficacy studies are needed.

From a clinical viewpoint, however, the gastroenterologist looks to the literature for guidance. The Tack study[1] was performed in patients seen at a tertiary referral centre; they had chronic IBS (mean duration of four years) and abdominal pain on 5.4 days per week; gastroenterologists have little to offer such patients if they have failed to respond to antispasmodic treatments.[26] This is where effectiveness rather than efficacy studies are needed.

In the largest cost effectiveness study of its kind, we found that paroxetine at low dose (20 mg/day) led to improved health related quality of life in the long term (15 months after entry) in comparison with usual treatment for patients with severe and treatment resistant IBS.[21] For patients who took the medication there were short term gains, compared with treatment as usual, in all five outcome measures (pain severity and frequency, distress severity, and mental and physical aspects of health related quality of life).[21] In the long term intention to treat analysis, there were benefits in health related quality of life that were not confined to those patients who had psychiatric disorders.[27]

The correct interpretation of this pragmatic cost effectiveness study was that in a clinically representative sample of people with severe IBS, which has not responded to usual treatment, considerable improvement in health related quality of life was achieved at no extra cost. The study was not designed to assess the mechanism of action but we did show that improvement in health related quality of life could not be explained solely on the basis of improved abdominal pain or improved mood.[21] It has been suggested that this long term result may have been the result of increased contact time with the gastroenterologist or general practitioner who prescribed paroxetine[28] but the additional time was minimal—it was not significantly greater than treatment as usual.[21] Thus in practice there is a gain for patients, in the aspect of the illness that concerns them most,[29] if gastroenterologists prescribe an SSRI antidepressant and encourage adherence.

Patients with IBS are a heterogeneous group. Of the 257 patients with severe IBS in our trial, 29% patients had depressive disorder and when this responded to treatment the number of days of restricted activity was nearly halved.[30] Another group (23%) had a history of sexual abuse (most did not have depressive disorder) and their health related quality of life improved greatly following either paroxetine or psychotherapy.[20] The improvement was not accompanied by improvement in mood or abdominal pain, suggesting this was not a non-specific result of increased contact time; it was mediated by marked improvement in somatisation.[20]

The exact mechanisms of action of SSRI antidepressants in IBS are not completely understood at this time. There may be several mechanisms which are important in different groups of patients. The antidepressant effect is important for those patients with depressive disorder. That apart, the most obvious next action is that involving changes in psychological processes, which lead to reduced somatisation and a reduced tendency to regard gut sensations as indicative of serious illness. These are very important actions in reducing treatment seeking. The SSRI antidepressants may also have important actions on the gut but at present these have not been adequately defined. The clinical practice of prescribing SSRI antidepressants in patients who have failed to respond to usual treatment is supported by our cost effectiveness data.

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PPARγ

Significance of anti-inflammatory effects of PPARγ agonists?

G Rogler

Peroxisome proliferator activated receptor γ expression in mucosal epithelial cells seems to be crucial for its anti-inflammatory effects with respect to experimental colitis, and for maintaining homeostasis of the mucosal barrier, at least in animal models

The peroxisome proliferator activated receptor γ (PPARγ) is one of three members of the PPAR family (PPARα and PPARδ), which itself is a part of the nuclear hormone receptor superfamily.[1–5] Nuclear hormone receptors are transcription factors that are activated by the binding of small lipophilic ligands.[6–11] They induce or repress transcription of a large number of different genes thereby influencing cellular functions.

PPARγ was initially identified for its role in adipocyte differentiation and regulation of genes involved in lipid and glucose metabolism.[12–15] However, activation of PPARγ also can antagonise nuclear factor κB (NFκB) action in macrophages resulting in downregulation of proinflammatory cytokines.[10 16–22] Implicated in these anti-inflammatory properties, PPARγ is not only expressed in adipocytes but also in a number of other cells types, such as macrophages,[9] lymphocytes, hepatocytes, and skeletal muscle. Very high expression levels are found in the colonic epithelium.[23]

Interestingly, the proinflammatory genes that are repressed by PPARγ overlap but are not identical to the genes that are downregulated by the glucocorticoid receptor (GR), another member of the nuclear hormone receptor superfamily which intracellularly mediates the effects of endogenous cortisol and therapeutically administrated glucocorticoids.[24] PPARγ mediated effects in the experimental setting of toll-like receptor stimulation were independent of NFκB and interferon regulatory factor, in contrast with GR action.[24] This indicates that glucocorticoids and ligands of PPARγ could have additive therapeutic effects.

The eicosanoids 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid as well as 15deoxy-Δ12, 14,-prostaglandin J2 have been identified as naturally occurring ligands of PPARγ.[3 25] Thiazolidinediones (TZDs) are high affinity synthetic ligands of PPARγ, frequently referred to as "PPARγ agonists".[26] TZDs are currently used as insulin sensitising agents in the treatment of type II diabetes mellitus.[26–28]

Due to the anti-inflammatory properties of PPARγ, the therapeutic efficacy of eicosanoids and TZDs has been evaluated in different models of inflammation.[6 29–34]

PPARγ has gained interest among gastroenterologists[35] as it was consistently demonstrated that PPARγ ligands reduced mucosal damage and prevented or downregulated the inflammatory response in several murine models of intestinal inflammation.[23 36–41] Recently, further evidence of an anti-inflammatory role of the TZD-PPARγ ligand rosiglitazone was found in interleukin (IL)-10 deficient mice in which rosiglitazone delayed the onset of colitis[42] and in trinitrobenezene sulphonic acid induced colitis in rats in which it reduced mucosal ulceration and TNF secretion.[43] Overexpression of PPARγ by an adenoviral construct in mucosal epithelial cells in mice was associated with amelioration of experimental inflammation.[44]

However, TZDs are not the only agents that could become important in terms of the therapeutic use of the effects of PPARγ. Activation of PPARγ by conjugated linoleic acids also protected mice from experimental colitis.[45] This effect was not seen in mice with colonic knockout of PPARγ. As linoleic acids in the gut are mainly food derived bacterial metabolites, this finding raised the possibility of positive effects of food supplements on intestinal inflammation mediated via PPARγ.[46] This linked PPARγ mediated effects with homeostasis of intestinal microflora and the epithelial barrier. In normal mucosa, PPARγ in intestinal epithelial cells could recognise luminal bacterial metabolites