PostScript

LETTERS

The role of the selective serotonin reuptake inhibitor citalopram in irritable bowel syndrome

We read with great interest the article by Tack *et al* on the effect of the selective serotonin reuptake inhibitor (SSRI) citalopram on symptoms in patients with irritable bowel syndrome (IBS) (*Gut* 2006;**55**:1095–103). The usefulness of the results of this study are however debatable. Several previous studies have investigated the effect of tricyclic antidepressants and SSRIs on functional gastrointestinal symptoms. Because of errors or lack of clarity in study design, inclusion of very selected patient populations and, above all, small sample sizes, their role in the treatment of patients with IBS in daily clinical practice remains unclear.

The study of Tack *et al*, as already correctly pointed out by Creed in his commentary (*Gut* 2006;**55**:1065–7), also suffers from major shortcomings in study design, poor description of study population and no information on whether or not subjects and physicians/investigators were blinded and, if yes, how.

Nevertheless, Creed claims that this study provides useful information on the effect of citalopram on the primary outcome measure—number of days per week with abdominal pain. What is relevant for patients as well as physicians is the risk of reduction in the number of days with abdominal pain after citalopram treatment. From the results of this study a relative risk of abdominal pain can be calculated: using data from the parallel group only (the first treatment episode), patients that used citalopram reported 3.7/7 = 53% of the week with abdominal pain compared with 5.2/7 = 74% of the week in patients receiving placebo. This results in a relative risk of 0.72 (95% confidence interval 0.58–0.89) for abdominal pain when using citalopram compared with placebo. This sounds very promising. However, when performing a post hoc power analysis for this study, with alpha being 0.05 and a minimally appropriate power of 80%, each treatment group should have consisted of at least 82 subjects. This means that this study was heavily underpowered and results should therefore be interpreted as for a pilot study.

Considering that there are already many studies available investigating the potential benefits of antidepressants in small samples of patients with IBS, this study does not contribute to the ongoing discussion about the role of antidepressants in the treatment of patients with IBS in daily clinical practice. There is still a need for a large, well defined, randomised, double blind, placebo controlled clinical trial to investigate the true effect of an antidepressant on symptoms in patients with IBS.

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Authors' response

We read with great interest the letter by Van Kerkhoven *et al* (this issue) concerning a recent article published by our group (*Gut* 2006;55:1095–103). We thank the authors for their interest in our work. In this study, we found that treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram markedly improves symptoms, including abdominal pain, compared with placebo in non-depressed patients with irritable bowel syndrome (IBS). Moreover, this effect on core IBS symptoms was found to be independent of effects on anxiety and depression as measured by self-report questionnaires.

We agree that there are several previous studies investigating the effect of tricyclic antidepressants on functional gastrointestinal disorders.[1 2] However, although SSRIs are widely used in the treatment of IBS in clinical settings, there is a paucity of randomised controlled trials studying their effectiveness in this indication, as pointed out in our study, by Dr Creed in his commentary to our study and also in recent excellent reviews regarding this topic.[1–3] Only four previous trials have been identified by Creed, and by ourselves in the Discussion section of the article. Moreover, we believe that this study may be important as it is one of the first to show a considerable effect not only on overall well-being and quality of life but also on core IBS symptoms including abdominal pain and bloating. Furthermore, this was observed in a study that excluded patients with high anxiety and depression levels.

We agree that this study has important limitations, as dealt with in the discussion section of the original article, and reiterated in the commentaries by Creed and in the letter by Van Kerkhoven *et al*. We agree that the analysis of the first phase as a parallel group design study in a smaller patient group and the recruitment of patients from a tertiary care setting are all limitations. However, the study was principally designed to provide mechanistic insight into the mode of action of SSRIs; it was not designed to be the definitive clinical study. Therefore, we excluded patients with high anxiety and depression levels and we performed assessments of the effect of the SSRI on colonic sensorimotor function. Hence, although the number of patients included in this demanding trial is small, the patients were exceptionally well characterised in terms of symptoms, colonic sensorimotor function and psychosocial profile. Moreover, the participation rate throughout the study remained high, and the study remained double blind throughout its long course. The cross-over design was also chosen to allow close correlation of (effects of citalopram on) colonic sensorimotor function and symptomatic outcome. As such, this study is the first one to show efficacy on core IBS symptoms, which cannot be attributed to peripheral effects in colonic sensorimotor function, nor to effects on anxiety, depression or somatisation.

It is crystal clear that this needs confirmation in a larger, placebo-controlled parallel group trial in a non-tertiary care setting, as we already indicated in the final sentence of the paper: ''Larger scale studies will be required to study the efficacy of citalopram or other SSRIs in the IBS patient population seen in primary practice and in secondary care''. When designing such a large trial, our study provides important insights on which symptoms to assess, what dose of citalopram to use, which symptoms respond over which time course of response, and shows that results can be obtained even when excluding patients with high anxiety or depression levels. However, it is generally extremely difficult to obtain funding for therapeutic trials in patients with functional bowel disorders with existing psychotropic drugs, and we believe this is the main reason that such information is lacking. If Van Kerkhoven *et al* were to succeed in organising such a large multicentre trial, we would be more than happy to contribute by including carefully selected and well-characterised patients with IBS.

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Mechanical lithotripsy for Bouveret's syndrome

We read with interest the editor's quiz about Bouveret's syndrome by Yau *et al* (*Gut* 2006;**55**:373, 387). We noted the comments that these cases are usually dealt with surgically, and carry a high morbidity. Recently, we had a similar case, which was managed without surgical intervention using mechanical lithotripsy as normally used at endoscopic retrograde cholangiopancreatography, avoiding the need for laparoscopic surgery.

A 79-year-old woman was admitted with a 2-month history of recurrent vomiting, abdominal pain and weight loss. A CT scan of the abdomen showed a grossly dilated stomach suggestive of gastric outlet obstruction due to stones in the second part of the duodenum (D2). A subsequent gastrografin follow through showed duodenal obstruction and a cholecystoduodenal fistula.

An oesophagogastroduodenoscopy showed an inflamed and narrowed pylorus with

malignant-looking ulcer and apparent gallstones in the D2. To relive the symptoms of obstruction, we wanted to remove the stones but the stones were too large to be moved in either antegrade or retrograde direction. Therefore, after dilating the pyloric stricture with a balloon, a mechanical lithotriptor was used to crush the stones, which were retrieved from the stomach with a Roth Net after being pulled back through the pyloric stricture.

The obstructive symptoms improved, but the biopsy specimens taken from the D2 confirmed the diagnosis of poorly differentiated adenocarcinoma of possible pancreatic origin and unfortunately she died 2 months after the admission.

Bouveret's syndrome was first described by Léon Bouveret in 1893 in *Revue de médecine*, where he reported two cases of this syndrome. It is a condition, that causes gastric outflow obstruction secondary to a gallstone impaction in the duodenum due to a cholecystodoudenal fistula. It is reportedly more common in women (65%). Typically, patients present with a few days' history of abdominal pain and vomiting but cases of haematemesis have been reported.[1] The stones could be seen on plain abdominal film or a CT scan along with pneumobilia and gastric dilatation.

The main aim of managing Bouveret's syndrome is to relieve the obstruction by removing the stones, which can either be done surgically or endoscopically. Obviously, it is preferable to avoid a surgical approach if possible because of the associated morbidity and mortality, which is 15–18% according to one study.[2] Therefore, endoscopic removal should be tried first before embarking on a surgical procedure. If the stones are large, as in our case, then laser[3] or mechanical lithotripsy[4] could be used to fragment the stones in the duodenum.

In the here-reported case, the patient had underlying incurable malignancy and was not fit for surgery to relieve the symptoms of duodenal obstruction; therefore, we fragmented the stones using a mechanical lithotriptor and then the small pieces were removed endoscopically. In summary, Bouveret's syndrome is a rare condition that needs to be treated endoscopically, if possible, using all available techniques including mechanical lithotripsy as many patients are not suitable for a more risky surgical procedure.

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Authors' response

We thank Afzal *et al* for their interest in reading our editor's quiz published in the March issue (2006) of *Gut* (2006;**55**(3):373, 387. An unusual cause of gastric outlet obstruction.)

We agree with Afzal *et al* that Bouveret's syndrome should be managed endoscopically first, if possible. However, most of the impacted gallstone is quite large and completely jammed inside the duodenum. It would be very difficult and even risky to introduce and deploy the mechanical lithotriptor. Endoscopic laser lithotripsy, therefore, has been tried by some endoscopists for fragmentation and piecemeal removal of an impacted gallstone.[1] Nevertheless, iatrogenic gallstone ileus after this endoscopic lithotripsy has been reported.[2]

Surgery will only be considered if these procedures failed to remove the gallstone. The major morbidity of conventional open enterolithotomy is related to the complications of its wound. Laparoscopic assisted[3] or even total laparoscopic enterolithotomy[4] can significantly decrease the size of the wound and should therefore be considered as the next treatment option when endoscopic retrieval of the gallstone failed.

Another valid point made by Afzal *et al* is to take biopsy from the fistula tract so as to exclude malignancy. However, even the presence of malignancy should not exclude any efforts made to relieve the gastric outlet obstruction, which is associated with considerable suffering.

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Bevacizumab and postponed suture leakages after surgery for ulcerative colitis and rectal cancer

Bevacizumab is a murine-anti-human monoclonal antibody directed against vascular endothelial growth factor-A, which disrupts endothelial cell survival mechanisms, and the recruitment and development of new tumour blood supply. Bevacizumab has been shown to prolong the duration of survival of patients with metastatic colorectal cancer when combined with chemotherapy.[1] Owing to its antiangiogenic properties, bevacizumab is also known to alter the healing process and to increase the rate of surgical wound healing complications, either in patients who underwent major surgery up to 2 months while receiving bevacizumab or in patients who started bevacizumab close to the date of a major surgical procedure.[2] We report the first occurrence of postponed suture leakages in a patient who had surgery for ulcerative colitis and was further treated with bevacizumab.

A 50-year-old woman with long-standing ulcerative colitis for 15 years underwent preoperative radiotherapy, followed by coloproctectomy, ileal pouch–anal anastomosis and diverting ileostomy for rectal cancer. The diverting ileostomy was transformed into an end-ileostomy 7 months later owing to a recurrent anastomotic ileovaginal fistula that was closed within 3 weeks. After 22 months, she presented with lung metastases. Treatment consisted of a fortnightly dose of irinotecan, folinic acid, and fluorouracil and bevacizumab combination. After the second cycle, she presented with a peristomial cutaneous dehiscence arising from the ileostomy circumference, and an anterior ileoanal anastomotic dehiscence that evolved through a 3-week period into the recurrence of the anastomotic ileovaginal fistula. Bevacizumab as well as chemotherapy were subsequently discontinued. Pouch endoscopy and biopsies did not show any features of pouchitis, and a punch biopsy targeted on the cutaneous edge of the healing peristomial dehiscence was unremarkable. Chemotherapy alone was reintroduced after a 4-week gap, and complete healing was assessed 2 months after the initial symptoms.

In this patient, the close temporal relationship that was observed between exposure to bevacizumab and the occurrence of suture leakages makes it likely that the drug was responsible. Interestingly, microcirculatory system abnormalities leading to chronic intestinal ischaemia,[3] as well as increased tissue and serum levels of vascular endothelial growth factor,[4 5] have been described in ulcerative colitis. These features may render patients with ulcerative colitis particularly susceptible to ischaemic complications in hypovascularised tissues such as digestive anastomosis or fistula scar when treated with an antiangiogenic therapy. Further observations are needed to confirm this hypothesis.

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