Symptomatic improvement of gastroduodenal Crohn’s disease with omeprazole

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K WOOLFSON, GR GREENBERG. Symptomatic improvement of gastroduodenal Crohn’s disease with omeprazole. Can J Gastroenterol 1992;6(1):21-24. Four patients with ileal Crohn’s disease presented with abdominal pain aggravated by food, a mean weight loss of 5.5 kg (range 4 to 7) and ulceration of the antrum and/or duodenum at gastroscopy, without radiological features of mechanical obstruction. The endoscopic and histological appearance of the ulcers was consistent with Crohn’s disease. Omeprazole 40 mg daily was administered, without other drugs, and after three days of therapy patients were asymptomatic. After eight weeks of omeprazole, a mean weight gain of 6 kg (range 3 to 10) occurred and the drug was withdrawn. One patient remained well and three patients relapsed, but all responded to long term omeprazole for up to three years. Follow-up endoscopies have indicated healing in one patient, partial healing in two patients and no change in one patient. Omeprazole may be of value in the symptomatic management of patients with gastroduodenal Crohn’s disease.

Key Words: Duodenal ulcer, ECL cells, Gastrin, H2-receptor antagonist

Amélioration symptomatic de la maladie de Crohn gastroduodénale traitée par l’éméprazole

RESUME: Quatre patients atteints de maladie de Crohn iléale ont rapporté des douleurs abdominales aggravée par les repas et une perte pondérale moyenne de 5.5 kg (4 à 7). L’examen gastroscopique a révélé des ulcérations de l’antre et du duodénum, sans signe d’obstruction mécanique. Les caractéristiques endoscopiques et histologiques semblaient concorder et indiquer une maladie de Crohn. Après trois jours de monothérapie par l’éméprazole (40 mg/jour), les patients étaient asymptomatiques. Après huit semaines, on a constaté un gain pondéral de 6 kilos (de 3 à 10) et mis fin au traitement. Les résultats se sont maintenus dans un cas; trois patients ont récidivé mais tous ont réagi favorablement à un traitement sous oméprazole prolongé jusqu’à trois ans. Le suivi endoscopique a permis de noter la guérison chez un patient, un rétablissement partiel chez deux patients et aucun changement chez le quatrième. L’éméprazole pourrait s’avérer utile dans le traitement symptomatique des patients porteurs d’une maladie de Crohn gastroduodénale.

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Crohn’s disease most commonly occurs in the terminal ileum and colon, but in 1 to 4% of patients there is also involvement of the stomach and duodenum (1-3). These patients have postprandial abdominal pain that often is similar to peptic ulcer disease, yet the majority lose weight, even in the absence of mechanical obstruction (1). Symptomatic improvement after administration of H2-receptor antagonists has been reported for patients with gastroduodenal Crohn’s disease (4), but frequently responses are incomplete and transient. Recent studies indicate that omeprazole, a potent inhibitor of gastric acid secretion, may be more efficacious for the management of patients with duodenal ulcer disease (5) and peptic oesophagitis (6). The present report describes four patients with nonobstructive active gastroduodenal Crohn’s disease in whom a trial of omeprazole therapy abolished pain and facilitated weight gain.

CASE PRESENTATIONS

Patient 1: A 24-year-old male diagnosed with Crohn’s disease at age 13 years who had undergone resection of the terminal ileum at age 20, presented with nausea, epigastric pain occurring 1 h postprandially and a 5 kg weight loss over eight weeks. At gastroscopy, there was one ulcer in the antrum, one ulcer in the pyloric channel and several aphthoid ulcers in the duodenum. The en-
endoscopic appearance was consistent with Crohn's disease and biopsies showed acute and chronic inflammation without granulomas. Ranitidine 300 mg bid was given and after four weeks the pain partially improved and a weight gain of 2 kg had occurred. At gastroscopy, there was a 25% healing of the gastric ulcers but the duodenal aphthoid ulcers remained; ranitidine therapy was increased to 300 mg tid. However, after 12 weeks of ranitidine therapy the pain had progressively worsened and there was a 7 kg weight loss. At endoscopy, the pyloric channel ulcer was larger and a new 1 cm ulcer in the duodenal cap was present; aphthoid ulcers in the duodenum remained. Biopsies showed acute and chronic inflammation without granulomas. Omeprazole 40 mg once daily was started and after 72 h therapy the patient was asymptomatic. After two weeks of omeprazole a 2 kg weight gain had occurred, but endoscopy showed persistent ulceration in the antrum and the duodenum. Omeprazole was continued for a further six weeks and then withdrawn. Within 72 h, nausea and abdominal pain recurred which again responded to omeprazole. After 12 weeks of omeprazole a weight gain of 10 kg occurred but endoscopic findings were unchanged. As further attempts to withdraw omeprazole caused recurrence of pain, this medication has been continued long term. After three years, the patient has remained asymptomatic with a total weight gain of 18 kg that has stabilized, although gastroscopy showed persistent but nonprogressive ulceration in the antrum and duodenum. Basal serum gastrin levels were 96 pmol/L (normal fasting values less than 30) and gastric biopsies have not shown enterochromaffin cell-like (ECL) hyperplasia.

**Patient 2:** A 22-year-old male presented with epigastric pain unrelated to food. An upper gastrointestinal barium radiograph identified a duodenal ulcer; therefore, the family practitioner administered ranitidine 150 mg bid. Failure of ranitidine to alleviate pain coupled with a 5 kg weight loss prompted referral. Gastroscopy showed multiple aphthoid ulcers in the first and second portions of the duodenum and marked duodenitis consistent with Crohn's disease. Biopsies revealed acute and chronic inflammation without granulomas. A subsequent small bowel enema identified nonobstructive Crohn's disease involving the terminal 15 cm of ileum; colonoscopy was normal. Ranitidine was increased to 300 mg tid and 5-aminosalicylic acid (Pentasa; Nordic Laboratories) 750 mg tid was started. After six weeks of therapy the abdominal pain was unchanged. Ranitidine was stopped, omeprazole 40 mg once daily was started and after 72 h the patient was asymptomatic. After four weeks of omeprazole a 1 kg weight gain had occurred, but endoscopic findings were unchanged. Omeprazole was continued for a further four weeks and, as the patient remained asymptomatic and weight had increased further 3 kg, the drug was withdrawn. After four days the abdominal pain recurred but responded again to omeprazole. As withdrawal of omeprazole on three subsequent occasions caused recurrence of pain, the medication has been continued for 18 months. The patient remains asymptomatic with a total weight gain of 7 kg that has stabilized, although at endoscopy multiple aphthoid ulcers remained in the duodenum. Basal serum gastrin levels were 71 pmol/L and gastric biopsies have not shown ECL cell hyperplasia.

**Patient 3:** An 18-year-old male developed Crohn's ileitis at age 16 years and was treated with sulphasalazine and prednisone. Subsequently, cimetidine was prescribed for duodenal ulceration identified at gastroscopy. The patient remained well for one year on no medication then presented with epigastric pain occurring 1 h postprandially and weight loss of 3 kg over two months. Gastroscopy revealed three prepyloric ulcers, one ulcer in the duodenal cap and one ulcer in the post bulbar duodenum; the pylorus was patent but lacked pliability. The endoscopic appearance was consistent with Crohn's disease and biopsies showed acute and chronic inflammation but no granulomas. Upper gastrointestinal radiographs showed no gastric outlet or duodenal obstruction. Ranitidine 300 mg bid provided only partial relief of pain and was increased to 300 mg tid. After 16 weeks of treatment a further 1 kg weight loss occurred and the ulceration was unchanged at gastroscopy. Ranitidine was discontinued and omeprazole 40 mg once daily was started; after 72 h of therapy abdominal pain was absent. After two weeks of omeprazole weight gain of 1 kg had occurred and at gastroscopy the prepyloric ulcers were reduced in size by 50% and aphthoid ulcers with mild duodenitis remained. After four weeks of omeprazole a further 2 kg weight gain had occurred and at gastroscopy the stomach was normal but persistent aphthoid ulcers with duodenitis remained. After eight weeks of omeprazole the patient remained asymptomatic, had a further 2 kg weight gain and at endoscopy only mild duodenitis was present. Omeprazole was discontinued and the patient has remained well with stable weight on no medication after three years of follow-up.

**Patient 4:** A 31-year-old female was diagnosed with Crohn's ileocolitis and severe perianal disease at age 29 years and, after one year of medical therapy, underwent a total colectomy. She had remained well without medication for one year and then presented with epigastric pain occurring 1 h after meals, retrosternal burning and a 6 kg weight loss over 14 weeks. At gastroscopy, there were three ulcers circumferentially arranged around the prepyloric antrum and a pyloric channel ulcer; the duodenum was normal. Biopsies showed acute and chronic inflammation without granulomas. Ranitidine 150 mg bid was started, but after two weeks of therapy there was no improvement and the dose was increased to 300 mg tid. After eight weeks of ranitidine therapy abdominal pain remained, bilious vomiting developed and endoscopic findings were unchanged. Biopsies showed acute and chronic inflammation and granulomas were identified. Omeprazole 40 mg once daily was started and after three days of treatment abdominal pain was absent. After four
weeks of omeprazole, a weight gain of 3 kg had occurred and gastroscopy showed that the prepyloric ulcers had reduced by 50%, but three new aphthoid ulcers were identified more proximally in the antrum, and aphthoid ulcers with duodenitis were now present in the duodenum. Omeprazole was continued for a further four weeks, and weight increased by 6 kg. As the patient was asymptomatic the drug was withdrawn. However, three weeks later the patient returned with nausea, epigastric pain and a 2 kg weight loss that again responded to omeprazole. Since subsequent withdrawal of omeprazole caused recurrence of pain, this medication was given long term. At 22 months of treatment the patient became pregnant; omeprazole was continued and the pregnancy was uneventful with the delivery of a healthy female. The patient remains asymptomatic after three years on omeprazole with stable weight, basal serum gastrin levels of 72 pmol/l; however, at endoscopy the prepyloric and duodenal ulceration was unchanged. Gastric biopsies have shown no ECL cell hyperplasia.

**DISCUSSION**

The four patients described with active Crohn's disease of the gastroduodenum and resistant to therapy with an H2-receptor antagonist showed symptomatic improvement and partial endoscopic regression after treatment with omeprazole. Consistent with other reports (1,3,7,8), Crohn's disease involving the stomach and/or duodenum was not always easily differentiated from conventional peptic ulceration. The present patients experienced similar symptoms of abdominal pain, although a contrasting feature was marked weight loss notwithstanding the absence of mechanical foregut obstruction.

Moreover, in accord with previous findings, histology was frequently not conclusive (3) as biopsy specimens showed granulomas in only one of the present patients. The endoscopic appearance of aphthoid lesions and their presence beyond the duodenal cap, coupled with identification of Crohn's disease elsewhere in the gut, have been suggested as the most important signs for the diagnosis of gastroduodenal Crohn's disease. In other series (4,7), Crohn's disease occurred in the distal small bowel and/or colon in 83 to 93% of patients presenting with involvement of the gastroduodenum. All four of the present patients had Crohn's disease elsewhere in the intestine, but in one patient ileitis was found only after the endoscopic appearance suggested the diagnosis of Crohn's disease.

Numerous approaches have been advocated for the treatment of patients with gastroduodenal Crohn's disease. Anti-ulcer regimen with H2-receptor antagonists and antacids were reported to provide symptomatic relief in five of 10 patients for two to nine months, but then corticosteroids were required (4). Other modalities including corticosteroids, singularly or in combination with total parenteral nutrition have been successful in the treatment of individual patients with gastroduodenal Crohn's disease (9-11). However, in a review of several series by Priebe and Simon (7) 23 of 30 patients ultimately came to surgery. Thus, any therapy that diminishes symptoms, facilitates weight gain and precludes the need for corticosteroids or surgery would be advantageous.

Omeprazole, a selective H'\(\mathrm{K}^-\)ATPase inhibitor is the most potent suppressant of gastric acid secretion currently available for use in humans (12). This drug provides rapid symptomatic relief for patients with conventional duodenal ulcer disease (5) and has become the agent of choice for management of patients with erosive peptic esophagitis (6) and the Zollinger-Ellison syndrome (13). These findings coupled with observations that pharmacological suppression of acid secretion might achieve symptomatic relief in patients with gastroduodenal Crohn's disease (4) provided the impetus for a trial of omeprazole therapy in the present patients. Symptomatic improvement with weight gain was rapid and sustained in all four patients, but importantly, none were mechanically obstructed. The mechanisms that accounted for the marked reduction of pain, which in turn facilitated food ingestion and weight gain, are not entirely clear. However, the specificity of omeprazole for binding to the parietal cell proton pump (12) does implicate, at least in part, a role for gastric acid.

In three of the patients there was only partial or no ulcer healing at endoscopy, however, none has shown progression of gastroduodenal disease. To maintain well-being in these patients, treatment with omeprazole has been required for up to three years. Concerns have been raised regarding the long term use of omeprazole in humans because, in rats, ECL cell hyperplasia and the subsequent development of gastric carcinoids has been reported (14). The causative mechanism for these observations is now known to be a trophic response to the sustained hypergastrinemia that, in turn, is related to the marked acid suppression by omeprazole (15). However, in humans, omeprazole administered for up to 24 months has not been associated with either ECL cell hyperplasia, or the development of gastric carcinoids (16). Similarly, in the present patients, there was no histological evidence for ECL cell hyperplasia. Serum gastrin levels have remained elevated by two- to threefold over values observed in healthy subjects, but notably the same magnitude of raised serum gastrin concentrations occurs in patients receiving H2-receptor antagonists long term, and without untoward effects. Although limited, the present experience with long term administration of omeprazole indicates an absence of side effects, but further evaluation with larger series of patients is clearly required.

In summary, four patients with non-obstructive gastroduodenal Crohn's disease showed symptomatic improvement with omeprazole. A therapeutic trial of omeprazole may be of value in similar patients prior to instituting corticosteroids or performing surgery.

**REFERENCES**

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