ARTHRITIS & RHEUMATISM
Vol. 42, No. 7, July 1999, pp 1545–1549

OCTREOTIDE TREATMENT OF CHRONIC INTESTINAL PSEUDOOBSTRUCTION SECONDARY TO CONNECTIVE TISSUE DISEASES

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Chronic intestinal pseudoobstruction (CIPO) is a rare syndrome that may occur in association with connective tissue diseases (CTD). Effective management is a major challenge. We report 3 cases in which subcutaneous octreotide was efficacious in the treatment of digestive symptoms in CIPO. In 2 of the 3 cases, previous treatment with domperidone, cisapride, or erythromycin had been unsuccessful. All 3 patients underwent a regimen of oral antibiotics along with octreotide to stimulate small bowel motility. The effects of octreotide were evident within 48 hours after the first injection in all patients. In 2, the efficacy seemed to decrease after 1 week and 6 months respectively, but increasing the dosage led to another remission. CIPO in CTD is a severe condition that can evolve regardless of the underlying disease activity. Octreotide appears to be efficacious in improving both clinical symptoms and manometric patterns. When its therapeutic effect diminishes, increasing the dosage can be useful.

Chronic intestinal pseudoobstruction (CIPO) is a rare clinical syndrome characterized by ineffective intestinal propulsion (1). It can be caused by an abnormality involving the visceral smooth muscle, the enteric nerves, or the visceral autonomic nervous system. It may be the primary disease or may be secondary to a recognized underlying disease. The causes of secondary CIPO are numerous and involve the nervous, endocrine, and metabolic systems, intraabdominal inflammation, infiltrative and connective tissue diseases (CTD), and drug-induced states (2). Since CIPO is a rare syndrome, medical and surgical treatments have yielded unsatisfactory results. Treatment efficacy is limited by lack of knowledge about the disease pathophysiology, lack of effective drugs, irreversibility of nerve and muscle damage in some patients, and the wide and often unknown extent of the effects in the gut (3).

It has been suggested that octreotide, a long-acting somatostatin analog, could improve small bowel motility in scleroderma (systemic sclerosis; SSc) (4–6) and in some patients with neuropathic abnormalities of the small bowel (7). However, there have been no published data on the long-term efficacy of this treatment, and the efficacy of octreotide in CIPO secondary to other CTD has not been evaluated. We report herein the effects of octreotide in the treatment of CIPO secondary to CTD (systemic lupus erythematosus [SLE], primary Sjögren's syndrome [SS], and SSc), with long-term followup.

CASE REPORTS

The clinical features and courses in the 3 patients are summarized in Table 1 and described below.

Patient 1. Patient 1, a 19-year-old woman, was hospitalized in December 1992 because of abdominal pain, vomiting, absolute food intolerance, and a 10-kg weight loss in 1 month. Plain abdominal radiography showed gaseous distention of the small bowel and fluid in bowel loops. Gastroscopy, colonoscopy, and small bowel series did not reveal mechanical obstruction. The most relevant laboratory findings were hemolytic anemia (hemoglobin 6.6 gm/dl), protein 57 gm/liter, albumin 33 gm/liter, proteinuria (>0.5 gm/24 hours), antinuclear antibodies (titer 1:320), positive anti-RNP and anti-SSA antibodies, and hypocomplementemia. Minor

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Submitted for publication November 25, 1998; accepted in revised form February 23, 1999.

Table 1. Main characteristics of 3 patients with chronic intestinal pseudoobstruction secondary to connective tissue disease, which responded to octreotide treatment*

	Patient 1	Patient 2	Patient 3
CTD	Primary SS	SLE	SSc
Age, years	19	52	70
Duration of CTD, years	0	36	21
Weight loss, kg	10	3	3
ANA titer	1:320	1:500	1:10,000
Small bowel manometry result	Absence of spontaneous phase III contractions; hypomotility; generation of low-amplitude phase III contractions after octreotide injection	Absence of spontaneous phase III contractions; generation of low-amplitude phase III contractions after octreotide injection	Not done
Years of followup after starting octreotide treatment	5	3	3

* CTD = connective tissue disease; SS = Sjögren's syndrome; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; ANA = antinuclear antibody.

salivary gland biopsy yielded a focus score of 2. Small bowel manometry performed during the fasting state showed low-amplitude phase III migrating motor complex (MMC) and antroduodenal hypomotility with weak distal antral, duodenal, and jejunal contractions. The postprandial pattern was characterized by almost total lack of contractions during the 2 hours of recording. Injection of 100 μg of octreotide subcutaneously generated phase III–like activity of MMC with low-amplitude contractions.

All of these findings were consistent with a diagnosis of CIPO. CIPO was considered to be secondary to SS, which had not previously been diagnosed. The patient was treated with intravenous methylprednisolone 1 gm/day for 3 days, followed by oral prednisone 1 mg/kg/day with total parenteral nutrition. There was no immediate improvement. In January 1993, a regimen of oral antibiotics along with octreotide (50 μg subcutaneously twice daily) was started. There was dramatic improvement within 2 days. Abdominal pain and vomiting disappeared. Oral feeding was resumed progressively with a low-residue diet, and parenteral nutrition could be stopped after 3 weeks. Prednisone was tapered after 2 months of digestive improvement. In December 1993, while the patient was still receiving prednisone at 6 mg/day, the results of small bowel manometry became normal and octreotide was stopped. There was no recurrence of CIPO after 4 years of followup.

Patient 2. Patient 2 was admitted to the hospital in April 1993 at the age of 52 because of abdominal pain, alternating diarrhea and constipation, subocclusion, vomiting, and significant abdominal distention. SLE had been diagnosed in 1957. Morphologic testing did not reveal mechanical obstruction. Pertinent laboratory findings included anti-RNP, antinuclear antibodies (titer 1:500), and anti-DNA antibodies (Farr assay 23%). She had been receiving treatment with prednisone 7 mg/day and hydroxychloroquine for her SLE. Cisapride (30 mg/day) was initiated, with no improvement in the symptoms. Small bowel manometry was performed during the fasting state and showed low-amplitude phase III MMC and antroduodenal hypomotility. The patient was discharged with enteral nutrition, oral antibiotics, and domperidone, but this treatment did not lead to remission.

A second small bowel manometry was performed in March 1995. There was no spontaneous phase III MMC. Nevertheless, subcutaneous injection of 100 μg octreotide generated phase III activity. Octreotide treatment was then continued at 50 μg twice daily. Within 48 hours, abdominal distention disappeared and gastrointestinal transit was normalized. However, these symptoms recurred 1 week later. Increasing the octreotide dosage to 200 μg twice daily led to remission. A third small bowel manometry performed in July 1996 yielded normal results. Octreotide, along with prednisone 6 mg/day and hydroxychloroquine, was continued. There was no recurrence of CIPO after 2 years of followup.

Patient 3. Patient 3, a 70-year-old woman, was hospitalized in September 1994 for intermittent bouts of intestinal obstruction. Limited SSc (CREST syndrome [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias]) had been diagnosed in 1973. Since 1993, she had been experiencing abdominal pain, vomiting, and constipation. Successive stimulation of gastrointestinal motility with cisapride and erythromycin did not improve the symptoms. Gastroscopy, colonoscopy, and small bowel series did not show

evidence of mechanical obstruction. Pertinent laboratory findings included the presence of antinuclear (titer 1:10,000), anti–Scl-70, anti–Jo-1, and anti–PM-1 antibodies. Before admission, treatment consisted of colchicine 1 mg/day. Octreotide 50 μg/day given subcutaneously was initiated. Abdominal pain and distention disappeared within 2 days, and digestive transit was normalized. In March 1995 the same digestive symptoms recurred, and the octreotide dosage was increased to 50 μg twice daily, with favorable results. After 3 years of followup, there was no relapse of digestive symptoms.

DISCUSSION

CIPO is a rare clinical syndrome resulting from ineffective intestinal propulsion due to reversible or irreversible dysfunction of either visceral muscle or enteric nerves that control visceral muscle. CIPO can have many underlying causes. It is well known that scleroderma can be complicated by CIPO (2,4). Fewer cases of CIPO in SLE and SS have been reported (8,9). SS was diagnosed in our patient 1 because of the presence of 5 of the 6 European Community criteria (10) (i.e., ocular symptoms, oral symptoms, ocular signs, focus score of ≥2 on minor salivary gland biopsy, presence of antinuclear antibodies, and presence of serum antibodies to SSA antigens). Patients 2 and 3 fulfilled the American College of Rheumatology criteria for the diagnoses of SLE and SSc (11,12), respectively. In all 3 patients, the presence of symptoms and signs of mechanical bowel obstruction in the absence of an occluding lesion of the intestinal lumen was in accordance with the criteria for CIPO proposed by Schuffler et al (2) and Christensen et al (3).

Management of CIPO is usually very challenging (13). Most reported experience is limited to case reports. Therapy should correct specific abnormalities leading to CIPO (i.e., blood electrolyte abnormalities, hormone disturbances, and side effects from drugs). Surgery has only very limited efficacy in improving transit and absorption along the intestine. Potentiation of cholinergic mechanisms has been widely used in patients with CIPO (3). Metoclopramide (14), domperidone (15), and cisapride (16) can stimulate antroduodenal motility and gastric emptying. It has also been shown that oral administration of cisapride can accelerate small intestinal transit. However, controlled studies did not show significant differences in symptom response in cisapride-treated versus placebo-treated patients (16). Neither of our patients receiving these drugs had improvement of their symptoms.

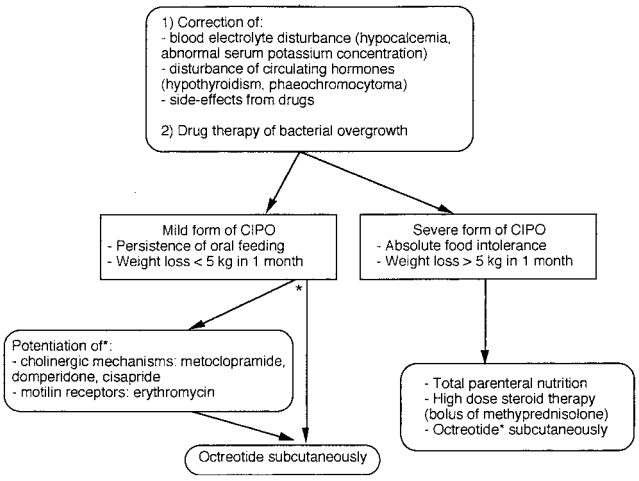


Figure 1. Algorithm for the treatment of chronic intestinal pseudoobstruction (CIPO) in patients with connective tissue disease. * = Drug selection for stimulation of gastrointestinal motility can be guided by the ability of the drugs to induce phase III–like migrating motor complex activity during small bowel manometry.

Erythromycin, which interacts with motilin receptors, has been shown to induce coordinated propulsive motor activity in normal subjects and in patients with diabetic gastroparesis (17). This effect appears with lower doses than are required for the drug's antibiotic action. Our patient 3 was treated with erythromycin with no improvement in her symptoms. It is possible that the oral route of erythromycin administration in a patient with gastric stasis and low absorption of erythromycin led to this negative result. However, although erythromycin-induced increases in gastric motility are known to occur, the action of erythromycin on small bowel motility has not been widely described.

Octreotide has been observed to both inhibit and stimulate phenomena associated with the interdigestive motility of the gut. The effect depends on the dose, route of administration, experimental model, and species (18). Octreotide can generate phase III MMC (19). In contrast, it can also inhibit gastric emptying (7) and antral and colon motility (20) and increase orocecal transit time. Whether this effect is achieved by a direct action on the intestinal muscle layer or by suppression of the release of intestinal peptide-like motilin is still a matter of controversy (18).

These various properties of octreotide may explain why there are only 2 published reports on its effect in CIPO secondary to CTD in a series of patients (4). In 1 uncontrolled study of 5 patients, octreotide showed efficacy in CIPO secondary to SSc (4). Another uncon-

trolled study showed that combined treatment with octreotide and erythromycin could improve some idiopathic and scleroderma-associated CIPO (6). Short-term administration of octreotide, 50 μg/day subcutaneously, stimulated intestinal motility in normal subjects and in patients with SSc, reduced breath hydrogen production, and improved abdominal symptoms. In our patients, manometry patterns showed hypomotility, suggesting a myogenic-type CIPO (21). Octreotide dramatically improved both digestive symptoms and manometric patterns.

Pharmacologic stimulation of intestinal motility by octreotide can sometimes generate phase III MMC, such as those observed during the recordings in our patients, which led us to prescribe this drug. Interestingly, the manometric improvement appeared within 2 hours after the first injection, and the time between the initiation of treatment and clinical improvement was also very short. All of our patients improved within 48 hours following the first octreotide injection. After a mean of 3 weeks of treatment, a decrease of treatment efficacy was suspected based on the recurrence of digestive symptoms. Increasing the octreotide dosage led again to remission. All patients had long-term improvement, and octreotide was discontinued in 1. No patient developed side effects, e.g., vomiting, diarrhea, abdominal pain, steatorrhea, or diabetes, during this long-term treatment with octreotide. Octreotide posology was chosen according to the dose that could generate phase III–like activity during small bowel manometry (4,6,9). It could be useful to identify the minimum effective dose for each patient.

In 2 of our 3 patients, the onset and evolution of CIPO was not parallel to that of the CTD itself. This explains why the treatment of the underlying disease (i.e., steroids, colchicine, hydroxychloroquine) was not modified. CIPO was the onset feature of primary Sjögren's syndrome in patient 1. Steroid therapy was started before pharmacologic stimulation of small bowel motility but did not improve the digestive symptoms until octreotide was started.

Taken together, these data suggest that octreotide should be used early in CIPO secondary to CTD. Use of other drugs, such as those that potentiate cholinergic mechanisms or stimulate motilin receptors, seems less efficacious in CIPO and does not dramatically improve symptoms. CIPO can be a very severe condition. We have previously reported that CIPO in CTD can sometimes lead to death (8,9). Moreover, our patient 1 experienced absolute food intolerance until octreotide was started. Long-term octreotide treatment is expensive, but its price could be reduced with the use of long-acting preparations such as long-acting octreotide or lanreotide. Treatment can also be modulated according to clinical presentation and to its efficacy (Figure 1).

The obvious efficacy of octreotide cannot be explained by a bias introduced by the retrospective nature of this study. In our department, CIPO secondary to SLE, SS, or SSc has been found in only 8 patients (9). Among these, the 3 patients described herein were hospitalized after 1993, when we began using octreotide to treat CIPO secondary to CTD. Remission was induced in these 3 patients within a few days following the initiation of treatment. The 5 other patients with CIPO secondary to CTD were hospitalized before 1993 (9) and were not treated with octreotide. They also sometimes had improvement of digestive symptoms, but this was not as clear and rapid as in the octreotide-treated patients. Immunosuppressive therapy using high-dose methylprednisolone, prednisone, and azathioprine was tried in these non–octreotide-treated patients, but was not successful.

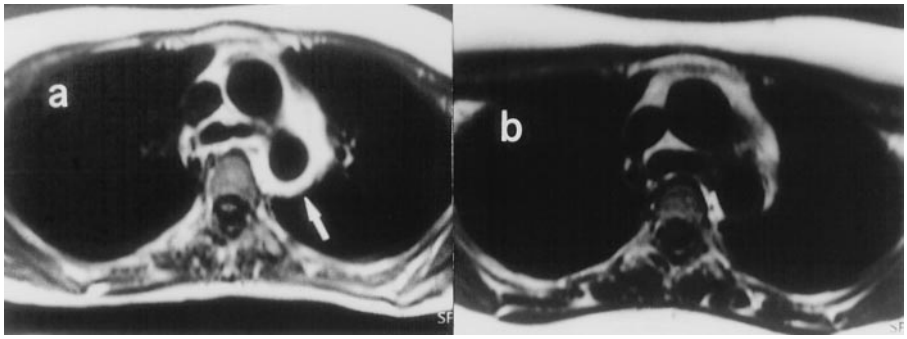
We conclude that CIPO in CTD is a severe condition that is reversible with treatment. CIPO can evolve even if the underlying disease is inactive. Most medical treatments have yielded disappointing results. Although the series of patients described herein is small and heterogeneous, our findings indicate that octreotide is the most efficient drug for rapidly improving both clinical symptoms and manometric patterns. When the therapeutic effect of octreotide declines, increasing the dosage can be useful. Long-term followup shows that improvement can extend for several years and that immunosuppression is not an obligatory means of treatment for CIPO secondary to CTD.

REFERENCES

1. Faulk DL, Anuras S, Christensen J. Chronic intestinal pseudoobstruction. Gastroenterology 1978;74:922–31.
2. Schuffler MD, Rohrmann CA, Chaffee RG, Brand DL, Delaney JH, Young JH. Chronic intestinal pseudo-obstruction: a report of 27 cases and review of the literature. Medicine (Baltimore) 1981;60:173–96.
3. Christensen J, Dent J, Malagelada JR, Wingate DL. Pseudoobstruction. Gastroenterol Int 1990;3:107–19.
4. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. N Engl J Med 1991;325:1461–7.
5. Owyang G. Octreotide in gastrointestinal motility disorders. Gut 1994;3 Suppl:S11–4.
6. Verne GN, Eaker EY, Hardy E, Sninsky CA. Effect of octreotide and erythromycin on idiopathic and scleroderma-associated intestinal pseudoobstruction. Dig Dis Sci 1995;40:1892–901.
7. Bassoti G, Germani U, Calcara C, Spinozzi F, Roselli P, Morelli A. Effects of octreotide on manometric variables in patients with

neuropathic abnormalities of the small bowel. Dig Dis Sci 1997; 42:1634–9.
8. Cacoub P, Benhamou Y, Barbet P, Piette JC, Le Cae A, Chaussade S, et al. Systemic lupus erythematosus and chronic intestinal pseudo-obstruction. J Rheumatol 1993;20:377–81.
9. Perlemuter G, Chaussade S, Wechsler B, Cacoub P, Dapoigny M, Kahan A, et al. Chronic intestinal pseudoobstruction in systemic lupus erythematosus. Gut 1998;43:117–22.
10. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome: results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.
11. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
12. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
13. Camilleri M. Appraisal of medium- and long-term treatment of gastroparesis and chronic intestinal dysmotility. Am J Gastroenterol 1994;89:1769–74.
14. Grandjouan S, Chaussade S, Couturier D, Thierman-Duffaud D, Henry JF. A comparison of metoclopramide and trimebutine on small bowel motility in humans. Aliment Pharmacol Ther 1989;3: 387–93.
15. Davis RH, Clench MH, Mathias JR. Effects of domperidone in patients with chronic unexplained upper gastrointestinal symptoms: a double-blind, placebo-controlled study. Dig Dis Sci 1988; 33:1505–11.
16. Camilleri M, Malagelada J-R, Abell TL, Brown ML, Hench V, Zinsmeister AR. Effects of six weeks treatment with cisapride in gastroparesis and intestinal pseudoobstruction. Gastroenterology 1989;96:704–12.
17. Annese V, Janssens J, Vantrappen G, Tack J, Peeters TL, Willemse P, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. Gastroenterology 1992;102:823–8.
18. Gyr KE, Meier R. Pharmacodynamic effects of Sandostatin® in the gastrointestinal tract. Digestion 1993;54 Suppl 1:14–9.
19. Haruma K, Wiste JA, Camilleri M. Effect of octreotide on gastrointestinal pressure profiles in health and in functional and organic gastrointestinal disorders. Gut 1994;35:1064–9.
20. John KD, Ballantyne GH, Modlin IM. Octreotide acetate inhibits motility in the rabbit distal colon. Eur Surg Res 1997;29:311–8.
21. Anuras S, Anuras J, Bozeman T. Small intestinal manometric studies in patients with familial visceral myopathies. J Gastrointest Motil 1990;2:190–3.

Clinical Images: Early diagnosis of Takayasu arteritis using gadolinium-enhanced magnetic resonance imaging



The patient, an 18-year-old woman, was admitted to the hospital with back pain of 5 months' duration. Ten days prior to admission, she had developed a fever of 38°C. On admission, her blood pressure was 110/60 mm Hg without laterality. Bruits over the right side of her neck and the epigastric region became audible 6 days after admission. Magnetic resonance angiography (MRA) and gadolinium (Gd)–enhanced magnetic resonance imaging (MRI) of the thoracic aorta were performed. Mural thickening of the descending aorta was visualized by Gd-enhanced MRI **(a) (arrow),** while no luminal changes in the MRA and digital subtraction angiography could be detected. The Gd enhancement of the aortic wall disappeared after treatment with prednisolone **(b).** Gd-enhanced MRI is useful in the diagnosis of Takayasu arteritis, especially in the early stage.

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