BRIEF COMMUNICATION

Octreotide for enterocutaneous fistulas of Crohn's disease

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Crohn's disease is a chronic, life-long disease and has many troublesome complications. Fistulas are a part of Crohn's disease, and although there are many therapeutic modalities used in treating these fistulas they are only partially successful. As we are still very far from being able to cure it, the aim is to improve the patients' quality of life and to reduce the iatrogenic harm that may be caused by various treatment modalities. Somatostatin is an inhibitor of intestinal secretion and has been used to treat pancreatic and surgical fistulas. Therefore, we decided to treat enterocutaneous fistulas using somatostatin.

METHODS: Five patients with Crohn's disease were treated with four daily injections of 300 µg octreotide. The total period of treatment was eight weeks.

RESULTS: Closure of fistulas was achieved in four of the five patients.

CONCLUSION: Somatostatin may have a role in treating Crohn's disease enterocutaneous fistulas and may prevent surgery or prolonged immunosuppressive therapy.

Key Words: *Crohn's disease; Enterocutaneous fistulas; Octreotide*

L'octréotide pour traiter des fistules entérocutanées de la maladie de Crohn

La maladie de Crohn est une maladie chronique et permanente qui s'accompagne de nombreuses complications pénibles. Les fistules font partie de la maladie de Crohn, et bien qu'il existe de nombreuses modalités thérapeutiques pour les soigner, celles-ci ne sont que partiellement efficaces. Comme nous sommes encore très loin de pouvoir guérir cette maladie, il faut viser à améliorer la qualité de vie des patients et à réduire les dommages iatrogènes susceptibles de découler de diverses modalités de traitement. La somatostatine est un inhibiteur de la sécrétion intestinale et est utilisée dans le traitement des fistules pancréatiques et chirurgicales. C'est pourquoi nous avons décidé de traiter les fistules entérocutanées à la somatostatine.

MÉTHODOLOGIE : Cinq patients atteints de la maladie de Crohn ont été traités au moyen de quatre injections quotidiennes de 300 µg d'octréotide. Le traitement a duré huit semaines.

RÉSULTATS : Les fistules se sont refermées chez quatre des cinq patients.

CONCLUSION : La somatostatine peut jouer un rôle dans le traitement des fistules entérocutanées de la maladie de Crohn et peut prévenir une chirurgie ou une thérapie immunosuppressive prolongée.

Fistulas are a part of Crohn's disease presentation. They are considered in three categories (1-7):

1. Benign or innocent;
2. Mild or "nuisance"; and
3. Complicated, associated with an abscess or intractable bowel disease.

Fistulas of the first category usually do not require treatment. Fistulas of the third category are mostly treated surgically (8). As for the second category, there are many therapeutic modalities with only partial success. Included in this category are enterovesicular, enterocutaneous and enterocolic fistulas. Most are treated with antibiotics and immunosuppressive drugs (9-13) for many months to achieve any result. For most of modalities the response rate is up to 60%, but relapse is common (14). Infliximab was shown to be effective in 67% of cases (15) but again, relapse rate is high because many patient develop tolerance or side effects. Results are somewhat better with combination therapy, but costs and side effects are higher.

It was demonstrated in animal models that regulatory peptides and cytokines play a role in the mucosal inflammatory process (16,17). The inhibitory neuropeptide vasoactive intestinal peptide levels were increased in Crohn's disease and it was also shown to inhibit proinflammatory cytokines in trinitrobenzene sulfonic acid-induced colitis (18). In another study, substance P immunoreactive nerves were found to be active in Crohn's disease. Substance P was shown to regulate somatostatin expression in inflammation (19).

In the human gastrointestinal tract, three different types of tissue compartments express somatostatin receptors; the gastrointestinal mucosa, the peripheral nervous system and the gut associated lymphoid tissue (20). In all of them, somatostatin binding is of high affinity and is specific for bioactive analogues.

Because somatostatin is an inhibitor of intestinal secretion (21-23) and has been tried in a wide variety of medical conditions (24-29) including pancreatic and surgical fistulas (30-33), we decided to use a relatively high dose to treat Crohn's disease enterocutaneous fistulas.

PATIENTS AND METHODS

Five patients with Crohn's disease and enterocutaneous fistulas were treated with octreotide. Each patient served as his own control, having each been treated with mesalazine and metronidazole

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TABLE 1
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Patient	Age (years)	Sex	Disease duration	Disease location	Fistula location	Cause	Treatment	Outcome
SK	17	Female	2 years	Terminal ileum	Abdomen	Postabscess drainage	Mesalazine Ciprofloxacin Metronidazole	Closed reopened surgery
MR	50	Male	30 years	Terminal ileum Right colon	Abdomen	Postoperative	Mesalazine Metronidazole 6-mercaptopurine Ciprofloxacin	Closed
AN	40	Male	26 years	Small and large bowel	Abdomen	Spontaneous	Metronidazole Ciprofloxacin	Closed
SM	37	Male	1 year	Ileum	Abdomen	Post abscess drainage	Ciproxin Metronidazole Mesalazine	Closed reopened one year later. surgery
TB	45	Male	6 years	Terminal ileum Rectum	Gluteal	Spontaneous	6-mercaptopurine Metronidazole	Closed

before. The patients were taught to subcutaneously inject 300 μg of octreotide four times daily. The dose was chosen according to previous partially successful reports for surgical fistulas (27-29). To demonstrate effect, we decided to give a relatively high dose in this pilot study. The patients were seen every week by the same physician and fistula was assessed according to pads used by the patient.

Other medications, including antibiotics, were not allowed. The total period of treatment was eight weeks. Results are shown in Table 1 and case reports are described below.

CASE PRESENTATIONS

Case one

A 17-year-old girl developed Crohn's disease of the terminal ileum at the age of 15. She was well on mesalazine for two years and then developed fever and a red tender spot in the right groin. Computerized tomography revealed inflamed small bowel loops with an abscess formation. This was punctured for drainage and later an enterocutaneous fistula developed. The patient was treated for three months with corticosteroids, ciprofloxacin, metronidazole and mesalazine, without response. She was then put on total parenteral nutrition for bowel rest, and after an additional two weeks, injections of somatostatin were added. Four weeks of treatment closed the fistula. Two weeks later an upper gastrointestinal series was done, following which the fistula reopened. She was sent for surgery and had terminal ileectomy. Since then, she has been doing well solely on mesalazine.

Case two

A 50-year-old man had Crohn's disease for 30 years. Five years after diagnosis, he had a terminal ileectomy and a right hemicolectomy due to an obstructive disease. Twelve years later he had another resection of the preanastomotic intestine for the same reason, following which an enterocutaneous fistula developed. He was treated with mesalazine, metronidazole, corticosteroids and 6-mercaptopurine for six months without improvement. Somatostatin was then added.

The fistula closed after five weeks and has remained closed for 24 months. The patient is currently taking mesalazine and 6-mercaptopurine.

Case three

A 40-year-old man was suffering from diffuse Crohn's disease for 26 years. At the age of 14 years he had a subtotal colectomy, followed by a short remission.

A year later he was sick again, necessitating prolonged periods of corticosteroids and mesalazine. An attempt to give him 6-mercaptopurine led to severe neutropenia. There was no response to methotrexate. At 21 years of age he underwent his second surgery, a gastrojejunostomy, because of obstruction due to Crohn's duodenal involvement.

Two years later he developed severe perianal disease and twice had perianal abscess drainage. At that time, he already had an anastomotic stricture, which was dilated at colonoscopy using through-the-scope balloon dilators. He developed an enterocutaneous fistula, originating in the preanastomotic ileum. He did not respond to three months of treatment with metronidazole and corticosteroids and was therefore started on somatostatin injections. After three weeks, the fistula closed. He completed eight weeks of treatment. The fistula has remained closed for 19 months, and the patient is currently taking mesalazine and intermittent corticosteroids.

Case four

A 37-year-old man was diagnosed as suffering from Crohn's disease involving most of the ileum. He was treated with mesalazine, but a year later he was hospitalized with fever and pain. Computerized tomography revealed abscess formation above the bladder. This was drained and he received antibiotics, corticosteroids and mesalazine. Removal of the drain resulted in ileocutaneous fistula formation. After two months of metronidazole, somatostatin injections were added and the fistula closed within two weeks. The patient completed eight weeks of treatment. He was maintained on mesalazine, but a year later his disease worsened and the fistula reopened. At

that time he was referred for surgery and had a resection of the cecum and a segment of distal ileum. He recovered uneventfully.

Case five

A 45-year-old man was suffering from Crohn's disease for six years. He had involvement of the terminal ileum and rectum together with an active perianal disease. He was treated with mesalazine, metronidazole and 6-mercaptopurine for six months, but developed a cologluteal fistula.

He was started on somatostatin injections and his gluteal fistula closed after six weeks. The patient complained of worsening diarrhea, but was able to complete eight weeks of treatment. The fistula has remained closed for twelve months, and the patient is currently taking mesalazine and 6-mercaptopurine.

Patient compliance and side effects

The patients were taught to inject themselves with somatostatin four times daily, and complied very well. Most of them tolerated the treatment well. Patient five complained of increased stool frequencies during treatment but he still completed eight weeks of therapy.

Acknowledging the reported complication of gallstones in patients receiving somatostatin (27-28), all patients were followed by an ultrasonographic examination. None developed gallstones. However, because of this feared complication, we chose not to prolong treatment beyond eight weeks.

DISCUSSION

Somatostatin is a cyclic peptide, consisting of 14 amino acids (31) with a variety of physiological activities. It is a neurotransmitter in the central nervous system and regulates growth hormone and thyrotropin release.

In the gastrointestinal tract, somatostatin has a mainly inhibitory action on glandular secretion, smooth muscle contractility, absorption of nutrients and activation of immune cells, as well as pancreatic secretion (34-35). It has been clearly shown to be present in inflammatory tissues.

Because of these qualities, somatostatin may be suitable for treating high to moderate output fistulas, which are troublesome to the patient. Several studies reported favourable results for both small bowel and pancreatic postoperative fistulas (36-38). In 1993, Torres et al (39) reported a double-blind study with 40 patients which found no significant difference in the percentage of fistula closures, following somatostatin treatment, compared with total parenteral nutrition. However, somatostatin shortened the time required for closure and reduced morbidity. In Crohn's disease, Skvarilova et al (40) reported results of intravenous somatostatin combined with total parenteral nutrition for the treatment of fistulas. The success rate was 37.5%. There are no details regarding dosage or duration of treatment. The authors also used histoacryl sealant as an additional treatment.

As Crohn's disease fistulas are related to disease activity, it may well be that somatostatin's favourable influence could be partially related to its role as an inhibitor of immune functions and, thus, act as a regulator of mucosal inflammation (41). Recent studies show that somatostatin acts on T-cells to regulate interferon-γ release (42,43), inhibits TNF-α in cell lines and regulates cytokine expression in human colonic epithelial cells (44), suppressing proinflammatory cytokines, such as monocyte chemoattractant protein-1, interleukin (IL)-8 and stimulating inhibitory cytokine IL-10.

The decreased concentration of somatostatin in inflamed colonic mucosa of inflammatory bowel disease patients could also suggest a role for it in the inflammatory process, which may explain in part our favourable results.

A paper by Present (14) summarized the current experience with Crohn's disease fistulas. The success rate with most therapies is approximately 60% with high recurrence and is involved with both high cost and high incidence of side effects.

CONCLUSIONS

Fistulas are common and occur in up to 35% of patients with Crohn's disease. They are very troublesome to the patient and markedly reduce quality of life; therefore, there should be a place for less toxic therapy such as somatostatin, whether as a bridge to surgery or while considering cytotoxic drugs. It may also be used for relatively inactive disease except for a fistula as a single symptom.

In a pilot study, we treated five Crohn's disease patients with enterocutaneous fistulas, giving relatively high doses of octreotide, the potent analogue of somatostatin (45), and four of them responded.

We suggest that somatostatin may have a role in treating Crohn's disease enterocutaneous fistulas and may prevent surgery or prolonged immunosuppressive therapy. Longer treatment should be considered as well as long-acting somatostatin analogues in an aim to achieve better results.

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