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Octreotide in malignant intestinal obstruction

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Octreotide has proved an effective agent in the palliation of refractory malignant intestinal obstruction. This may be achieved through a pro-absorptive effect on the small bowel mucosa, an effect on improving gastrointestinal motility, by a reduction in gastrointestinal hormone levels and by a direct anti-neoplastic effect on the obstructing tumour. The simple route of administration of octreotide and the paucity of side effects reported in two recent studies should make the physician consider its use in this particularly distressing complication of advanced cancer.

Key words: Intestinal obstruction, malignancy, octreotide, palliation.

Introduction

Intestinal obstruction is a distressing and often fatal complication of advanced malignancies. Palliation of symptoms from obstruction has not been achieved satisfactorily with drug treatment and has traditionally led to the patient being admitted to hospital for nasogastric suction and intravenous fluid replacement. The antitrophic hormone Somatostatin and its long-acting analogue octreotide may be useful in this cohort of patients. There is evidence that octreotide is effective in palliating the symptoms of malignant bowel obstruction. This may be achieved through a proabsorptive effect on the small bowel mucosa, an effect on improving gastrointestinal motility, by a reduction in gastrointestinal hormone levels and by a direct anti-neoplastic effect on the obstructing tumour. In this review we discuss the evidence for these multiple modes of action and appraise two recent clinical trials that have used subcutaneous octreotide for this specific purpose.

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Malignant bowel obstruction

Gastrointestinal obstruction is a frequent terminal event in a number of disseminated cancers. The basic treatment of small bowel obstruction, regardless of aetiology, has not changed significantly in 50 years.[1] The obstruction may be partial or complete and produces symptoms that are often extremely unpleasant, difficult to palliate effectively and make the quality of the patient's remaining life very poor. It is a common problem associated with advanced malignancies, particularly in patients with ovarian and colorectal carcinoma, and presents classical symptoms of abdominal pain, abdominal distension, nausea, vomiting and constipation. The symptoms may occur suddenly or have a more insidious onset; they be constant or intermittent and may wax and wane in severity. Bowel obstruction is often the terminal event in this group of patients. The causes of obstruction include relapse and/or local advancement of intrabdominal primary or secondary tumour, diffuse peritoneal carcinomatosis, bowel encasement by tumour, or multiple partial occlusions of the lumen of the bowel which delay or prevent the distal propulsion of intestinal contents. Rarely, the underlying cause may actually be benign, such as postoperative adhesions occurring after primary or palliative surgery or exacerbated by the use of opiates for pain originating outside the abdomen.

The management of intestinal obstruction in advanced cancer patients remains a controversial topic. Surgical intervention is considered after weighing up the risks of further morbidity from surgery. In this situation the patients themselves may refuse surgery or may not be fit for anaesthesia. Conventionally, the patient is hospitalized to facilitate nasogastric suction and intravenous fluid replacement. However, the majority of patients have incomplete obstruction and may respond to drug treatment with a regular oral intake of food and fluids aimed at keeping the intestinal contents

soft, reducing gastrointestinal secretions, controlling vomiting and preventing bowel spasm.

Vomiting due to intestinal obstruction related to malignancy is managed usually by resting the bowel to reduce secretions and bowel spasm. Medical management includes the use of anti-emetics, high-dose steroids, antispasmodic agents and analgesics. The use of opiates may further increase the obstructive tendency and drugs such as metoclopramide and domperidone may cause increased discomfort and colic. Combinations of morphine with hyoscine and haloperidol have proved useful, particularly with their antisecretory effects.

Octreotide, the synthetic analogue of somatostatin, has been used recently for palliating symptoms secondary to malignant bowel obstruction. Two recent studies have shown a beneficial effect in the palliation of symptoms and there are experimental data that may explain the mechanisms of action and efficacy of this drug in the clinical setting.

Actions of octreotide

Somatostatin is a cyclic tetradecapeptide that is widely distributed within the nervous system and gastrointestinal tract. In the intestine, somatostatin is predominantly found in neural and mucosal neuroendocrine cells.[2] Gastrointestinal actions include inhibition of the release of gastrin, vasoactive intestinal peptide (VIP), secretin, insulin, and glucagon; reduction of pancreatic bicarbonate and enzyme secretion; inhibition of intestinal motility; and reduction of mesenteric blood flow.[3] Its action at a cellular level accounts for this broad spectrum of activity. The improved electrolyte absorption and the reduction in intestinal fluid secretion have led to the success of this agent in palliative care, as shown by a number of clinical trials. Octreotide may thus break the cycle of excess fluid secretion after obstruction and distension of bowel which otherwise may lead to necrosis and perforation.

Octreotide is extensively metabolized in the liver, with up to 30–40% hepatic extraction in healthy humans. The plasma elimination half-life ranges from 72 to 113 min and in most studies total body clearance is achieved in a mean of 11.4 h.[3] The development of octreotide has led to effective treatment of a number of gastrointestinal conditions which have, in turn, led to its use in malignant bowel obstruction. Octreotide is effective in reducing output from fistulas from the pancreas and small intestine within 48 h which would otherwise be refractory to conservative treatment with bowel rest and total parenteral nutrition.[4] In severe refractory secretory diarrhoea, 600 μg octreotide per day has decreased ileostomy stool output and removed the necessity for parenteral nutritional support.[5] In cryptosporidial diarrhoea in immunosuppressed patients such as those with AIDS, intravenous or subcutaneous octreotide in doses of 1800 μg/day for periods of up to 8 months have markedly reduced symptoms and allowed weight gains to occur.[6] In patients with the carcinoid syndrome, 100–600 μg octreotide per day have improved diarrhoea and flushing and reduced 24-h output of 5-hydroxyindoleacetic acid for up to 18 months.[7]

Patients with pancreatic tumours secreting vasoactive intestinal polypeptide (VIPomas) have high levels of VIP and pancreatic polypeptide. Octreotide reduces levels of VIP, although these may still be above normal. In an intestinal perfusion study in a patient with a VIPoma, Edwards *et al.*[8] showed that subcutaneous octreotide at 50 μg every 6 h increased fluid and electrolyte absorption in both the jejunum and ileum. This effect was due to both a reduction in hormone output and a further direct effect on intestinal and pancreatic fluid and electrolyte transport. In the clinical setting, dramatic and lasting palliation of the severe diarrhoea associated with this secretory tumour have been achieved with doses of 50–1500 μg/day for up to 38 months. Rapid symptomatic relief has been associated with a reduction in serum VIP levels. Octreotide has been shown to improve fluid and electrolyte balance in these patients and has removed the necessity for oral or intravenous fluids, with a resulting improvement in quality of life.

There is considerable experimental evidence for the beneficial effects of somatostatin and its analogues in patients with malignant bowel obstruction. It is now clear that the sites of action of this drug include the intestinal mucosa and intestinal musculature and, in addition, a specific anti-neoplastic effect in the obstructing tumour.

Octreotide in experimental small bowel obstruction in mice and evidence for a proabsorptive effect

The lack of a suitable experimental model to use in studying the physiological consequences of malignant bowel obstruction, and specifically the

effects of octreotide, have led to studies on animal models of mechanical intestinal obstruction instead.

Gittes *et al.*[9] performed bowel ligation at two sites, causing complete small intestinal obstruction, and evaluated the effects of octreotide on intestinal secretion. The ligation was achieved by proximal (ligament of Trietz) or distal (ileocaecal valve) suture in 160 male C57 strain mice. After 8 h the mice were randomly allocated to treatment with subcutaneous octreotide at 100 μg/kg every 8 h or 2 ml saline as a control. Survival of the mice was recorded as a definitive end-point, being easier to assess than bowel distension or radiological studies. In the proximal obstruction group, comprising 54 randomized mice, octreotide delayed death significantly by life-table analysis, giving a mean survival of 41 ± 4 h compared with 31 ± 3 h in control mice ($P < 0.003$ by unpaired t-test); 36 h after the obstruction, 11 out of 27 treated mice and 4 out of 27 controls were still alive ($P < 0.068$ by χ^2-test). By contrast, in the distal obstruction group, comprising 47 randomized mice, there was no statistical difference between those given octreotide or saline, the mean survival being 60 ± 5 versus 54 ± 4 h in controls.

A number of mechanisms were postulated to explain the improvement in the first (proximal ligation) group. Octreotide inhibits secretion from the gastric fundus, pancreas and small bowel. These secretions normally add to the intraluminal volume of secretions. In a vicious cycle, small bowel distension further stimulates intestinal epithelial secretion. The octreotide treatment inhibits gut secretion to alleviate this. Dharamsathaphorn *et al.*[10] have demonstrated stimulation of sodium and chloride absorption by somatostatin in rabbit ileum *in vitro*; this effect has also been demonstrated with the administration of octreotide. Furthermore, octreotide is known to inhibit gut hormone release; VIP has been implicated in the pathophysiology of small bowel obstruction,[11] and VIP levels respond dramatically to octreotide in patients with VIPomas, as discussed above.

Evidence for a direct proabsorptive effect of octreotide on ionic transport in the small intestine has come from a study by Anthone *et al.*[12] on rabbit ileal segments. In this study both octreotide and somatostatin infused arterially *ex vivo* caused a significant proabsorptive response in the fluxes of sodium, water and chloride during the period of drug infusion, which returned to basal secretory levels during the recovery period. The proabsorptive effect of octreotide observed in this study may be explained by: (1) the inhibition of secretory agonists known to stimulate adenylate cyclase, or directly decrease intracellular levels of cyclic AMP, by receptor activation of the inhibitory GTP-binding subunit of adenylate cyclase;[13] or (2) alterations in the intracellular concentration of calcium, which has a fundamental role in the control of intestinal transport under basal and stimulated conditions. Calcium may be another mediator since somatostatin can inhibit chloride secretion from rat colon via a chloride-regulated mechanism.[14]

Octreotide and gastrointestinal dysmotility

The proposed mechanism of action of octreotide is a direct effect on mucosal secretion reduction, and prolongation of transit time through the small bowel. There are few studies of gastrointestinal dysmotility associated with cancer. In normal subjects, somatostatin initiates an intense propagative pattern of motor stimulants in the duodenum, with a shortened length cycle of 40 min.[15] The observation that octreotide evokes a similar intestinal pattern of contraction in dogs suggested that this peptide might be beneficial in the treatment of small bowel dysmotility.[16] In a study of normal volunteers and patients with intestinal pseudo-obstruction due to scleroderma, a condition associated with chaotic and non-propagative small bowel motor activity, Owyang[17] showed that the administration of 100 μg subcutaneous octreotide induced propagative duodenal phase III complexes in both groups of subjects. The complexes propagated in the patients at the same velocity as in the normal subjects, and had two-thirds the amplitude of the spontaneous complexes in normal subjects (Figure 1). Small bowel bacterial overgrowth secondary to chronic pseudo-obstruction, which may also become a significant factor in cancer-related bowel obstruction, was also eliminated in the patients with scleroderma, as assessed by an improvement in clinical symptoms and objective improvement measured by hydrogen breath testing.

Anticancer effect of octreotide

Somatostatin is a hormone that is known to interact with normal and neoplastic cells. Octreotide binds to specific somatostatin receptors that are coupled to a variety of signal transduction pathways including tyrosine phosphatase. Data are accumulating to support the antimitogenic effects of

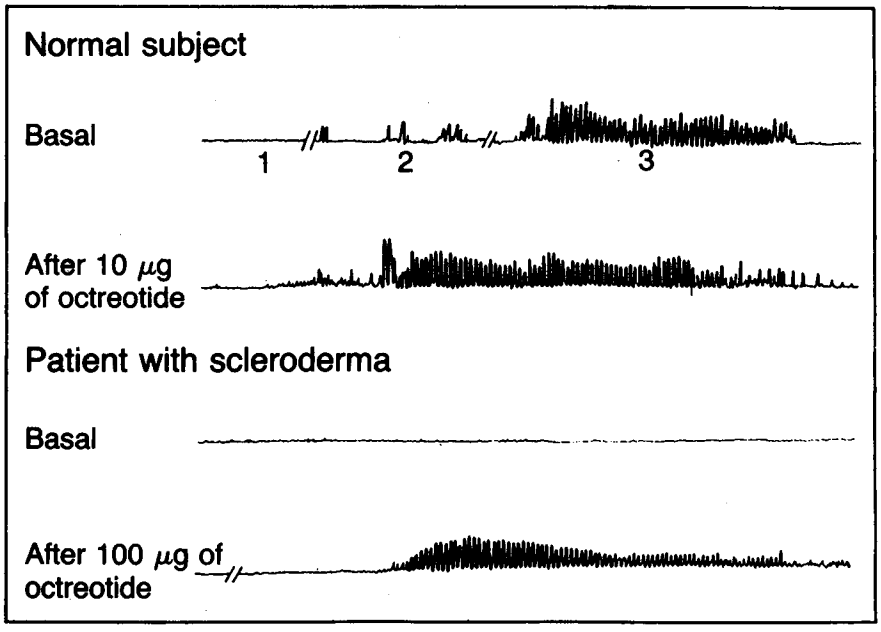

Figure 1. Intestinal manometric tracings in a normal subject and a patient with scleroderma. The normal subject showed a cyclic progression from the motor quiescence of phase 1 through phase 2 to the intense activity of phase 3, and octreotide (10 μg) stimulated phase 3 activity that was qualitatively similar to the spontaneous phase 3 activity. In the patient with scleroderma with pseudo-obstruction, normal migrating complex cycling was absent, and octreotide (100 μg) induced intestinal phase 3 activity qualitatively similar to that in the normal subject. Published with permission.[17]

octreotide, which may explain, at least in part, the success of octreotide in palliating malignant bowel obstruction. Stimulation of somatostatin receptor subtypes SSTR1 and SSTR2 has been implicated in the inhibition of cell proliferation *in vitro*.[18] Accordingly, octreotide has inhibited the basal and gastrin-stimulated growth of several human colon cancer cell lines *in vitro*.[19] In other studies, the growth and development of hepatic metastases have been reduced by somatostatin analogues,[20] and patients with refractory gastrointestinal cancer have shown a significant objective symptomatic response and survival benefit when treated with octreotide.[21]

Clinical studies

There have been two recent reports on pilot studies of patients with a variety of underlying neoplasms that resulted in bowel obstruction due to malignancy. Treatment with injections or infusions of octreotide subcutaneously were used in both studies.

Khoo *et al.*[22] studied 24 patients, all of whom had a prognosis of less than 2 months. The diagnosis of obstruction was made on the basis of clinical symptoms of vomiting, constipation, abdominal pain, signs of abdominal distension with obstructive bowel sounds, plus radiological evidence where available. Octreotide was used at 50 μg as a subcut injection or infusion every 8 h until vomiting had subsided, increasing in 50-μg steps every 8 h. The results are shown in Figure 2. Fourteen out of the 24 patients showed a complete response, with resolution of the bowel obstruction, and four showed significant improvement of symptoms. The median duration of treatment was 9.4 days (range 1–90 days) and the control of vomiting was rapid, occurring within 4 h of the administration of octreotide. In eight of the responding patients the final dose was increased from 125 μg (range 100–600 μg) to a median of 300 μg (200–700 μg). Seven patients did not respond despite doses of between 600 and 1200 μg/24 h. It was evident that if a response had not occurred with a dose of 600 μg there was no additional benefit by increasing the dose of octreotide. There was no toxicity from the treatment.

Mercadante *et al.*[23] studied 14 patients with a diagnosis of bowel obstruction made on radiological and clinical grounds as described in the previous study. Octreotide was given as a subcutaneous bolus or infusion at doses of 300–600 μg/24 h. Ten out of the 14 patients showed a complete response to treatment, with resolution of all obstructive symptoms, and two improved symptomatically. The median duration of treatment was 17.5 days (range 3–53 days). Side effects included pain at injection

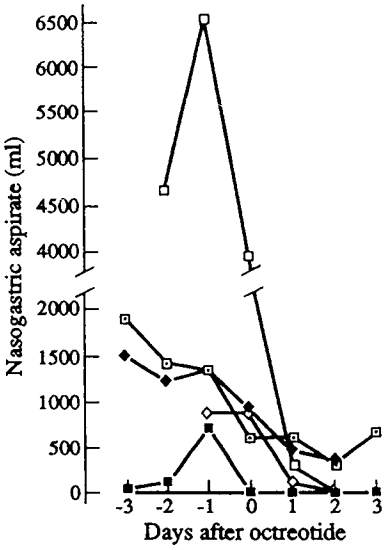

Figure 2. Nasogastric aspirate of obstructed patients during treatment with octreotide. Each line represents one patient. Published with permission.[22]

sites in seven out of 14 and non-specific rash in one patient; this did not require withdrawal of the drug.

The most frequent side effects reported by patients on octreotide for any indication have been pain at the injection site, abdominal cramps, nausea, bloating, flatulence, diarrhoea and steatorrhoea. The inhibition of glucagon and insulin production may thus cause a deterioration in glucose tolerance and lead specifically to vomiting; this was not recognized as a complication in either of these studies.[23]

Conclusions

Octreotide is an effective agent in the palliation of refractory malignant intestinal obstruction. This may be achieved through a proabsorptive effect on the small bowel mucosa, an improvement in gastrointestinal motility, a reduction in gastrointestinal hormone levels and a direct anti-neoplastic effect on the obstructing tumour. The simple route of administration of octreotide and the paucity of side effects reported in two recent studies suggests its use in this particularly distressing complication of advanced cancer.

References

1. Baines M, Oliver DJ, Carter RL. Medical management of intestinal obstruction in patients with advanced malignant disease. *Lancet* 1985; **ii**: 990–993.
2. Wilson J. Endocrinology and metabolism. In: Wilson J, Isselbacher KJ, Braunwald E, Wilson J, eds. *Harrison's principles of internal medicine.* New York: McGraw-Hill, 1994: 1898.
3. Battershill P, Clissort S. Octreotide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in conditions associated with excessive peptide secretion. *Drugs* 1989; **38**: 658–702.
4. De Bois MHW, Bosman CHR, De Graaf R, *et al.* Closure of a high-output pancreatic external fistula by SMS 201-995. *Neth J Med* 1988; **32**: 293–297.
5. Jaros W, Biller J, Greer S, *et al.* Successful treatment of idiopathic secretory diarrhoea of infancy with SMS 201-995. *Gastroenterology* 1988; **94**: 189–193.
6. Cook DJ, Kelton JG, Stanisz AM, *et al.* Somatostatin treatment for cryptosporidial diarrhoea in a patient with the acquired immunodeficiency syndrome. *Ann Intern Med* 1988; **108**: 708–709.
7. Kvols LK, Moerfil CG, O'Connell MJ, *et al.* Treatment of the malignant carcinoid syndrome: evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986; **315**: 663–666.
8. Edwards CA, Cann PA, Read NW, *et al.* The effect of somatostatin analogue SMS 201-995 on fluid and electrolyte transport in a patient with secretory diarrhoea. *Scand J Gastroenterol* 1986; **21** (suppl 119): 259–261.
9. Gittes G, Nelson MT, Debas H, *et al.* Improvement in survival of mice with proximal small bowel obstruction treated with octreotide. *Am J Surg* 1992; **163**: 231–233.
10. Dharamsathaphorn K, Binder HJ, Dobbins JW, *et al.* Somatostatin stimulates sodium and chloride absorption in the rabbit ileum. *Gastroenterology* 1980; **78**: 1559–1565.
11. Basson MD, Fielding LP, Bilchik AJ. Does vasoactive intestinal polypeptide mediate the pathophysiology of bowel obstruction? *Am J Surg* 1989; **151**: 109–115.
12. Anthone G, Bastidas JA, Orandle M, *et al.* Direct proabsorptive effect of octreotide on ionic transport in the small intestine. *Surgery* 1990; **108**: 1136–1142.
13. Koch BD, Schonbrun A. The somatostatin receptor is directly coupled to adenylate cyclase in GH4C, pituitary cell membranes. *Endocrinology* 1984; **114**: 1784–1790.
14. Schofield JG, Bicknell RJ. Effects of somatostatin and verapamil on growth hormone release and ^{45}Ca fluxes. *Mol Cell Endocrinol* 1978; **9**: 255–268.
15. Peeters TL, Janssens J, Vantrappen GR. Somatostatin and the interdigestive migrating complex in man. *Regul Pept* 1983; **5**: 209–217.
16. Peeter TL, Romanski KW, Janssens J. Effects of the long-acting somatostatin analogue SMS 201-995 on small intestinal interdigestive motility in the dog. *Scand J Gastroenterol* 1988; **23**: 769–774.
17. Owyang C. Octreotide in gastrointestinal motility disorders. *Gut* 1994; suppl 3: S11–S14.
18. Buscail L, Delesque N, Esteve JP, *et al.* Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin analogues: mediation by receptor subtypes SSTR1 and SSTR2. *Proc Natl Acad Sci USA* 1994; **91**: 2315–2319.
19. Dy D, Whitbread RH, Morris DL. SMS 201-995 inhibits *in vitro* and *in vivo* growth of human colonic cancer.

Cancer Res 1992; **52**: 917–923.
20. Nott DM, Baxter JN, Yates J, *et al.* Effects of somatostatin analogue SMS 201-995 on the growth and development of hepatic tumour derived by intraportal injection of Walker cells in the rat. *Br J Surg* 1989; **76**: 1149–1151.
21. Cascinu S, Del Ferro E, Catalano G. A randomised trial of octreotide vs best supportive care only in advanced gastrointestinal cancer patients refractory to chemotherapy. *Br J Cancer* 1994; **71**: 97–101.
22. Khoo D, Hall E, Motson R, *et al.* Palliation of malignant intestinal obstruction using octreotide. *Eur J Cancer* 1994; **30A**: 28–30.
23. Mercadante S, Caraceni A, Simonetti MJ. Octreotide in relieving gastrointestinal symptoms due to bowel obstruction. *Palliative Medicine* 1993; **7**: 295–299.