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Octreotide in the management of treatment-related diarrhoea

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Octreotide appears to have a major therapeutic effect in the management of diarrhoea related to cancer therapy. This effect is seen in the acute diarrhoea following radiation therapy and chemotherapy, and also in late radiation enteritis. As well as providing improved symptom control, early treatment can prevent potentially important morbidity in patients who are vulnerable to infection and fluid loss. Patients who suffer diarrhoea as a complication of AIDS, graft-versus-host disease and tumour-related diarrhoea can also obtain major benefit from treatment with octreotide. It should be considered as a first-line treatment in patients for whom diarrhoea may be a serious complication.

Key words: Diarrhoea, cancer, octreotide, radiation enteritis.

Introduction

Many cancer patients experience treatment-related diarrhoea, particularly those who are undergoing abdominal radiation therapy, or cytotoxic chemotherapy. Usually, it amounts to a transient but unpleasant symptom, and is self-limiting. However, in patients with poor performance, treatment-related diarrhoea can be a real threat, producing dehydration, malabsorption and a portal for infection. An awareness of patients at special risk, and attention to detail in planning treatment can minimize the risks of this treatment complication, but it will inevitably be encountered by physicians treating the abdomen with radiotherapy, or using certain cytotoxic drugs. When diarrhoea occurs, effective medical treatment is needed to control symptoms and minimize the associated risks.

In addition to acute and transient diarrhoea a separate subgroup of patients treated with radical intent, and with radical doses, will develop chronic diarrhoea and bowel dysfunction due to radiation enteritis. Until now, this has proved to be a very difficult complication to treat, and both medical and surgical measures have been of rather limited benefit.

The development of drugs that modulate the activity of gut-regulatory peptides, notably octreotide (Sandostatin), has allowed a new approach to the treatment of these symptoms. This review is concerned with the aetiology of treatment-related diarrhoea, and the place of octreotide (Sandostatin) in its management.

Radiation enteritis

Some degree of radiation enteritis is almost always present in patients receiving radical radiation therapy to the abdomen and pelvic organs. An acute reaction may occur with doses exceeding 10 Gy, and although symptoms generally become evident within 2 weeks of irradiation, their development may be delayed for as much as 2 months. Acute radiation enteritis is manifested by diarrhoea, tenesmus, and sometimes bloody stools. Where the radiation tolerance of the small intestine has been exceeded, griping pain may occur. This sign may indicate a risk of the subsequent onset of late radiation enteritis, which can be an intractable and serious complication. There are ways of reducing the incidence of such intestinal damage, namely the early recognition of patients at special risk, and attention to technical aspects of radiation dosimetry.

The pathological changes seen in acute radiation enteritis are due to damage to the rapidly proliferating cells located in the walls of the crypts of the bowel mucosa. Because of the high turnover of these cells, radiation damage is expressed very early, and after surprisingly low doses of radiation. Initial cell loss is followed by atrophy of the villi, and destruction of the normal crypt architecture. These changes are quantitatively related to radiation exposure, and are the basis of animal models used for radiobiology.[1–3]

Certain patients are at high risk of developing complications. These include patients receiving high-dose radiotherapy for gynaecological malig-

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nancies, especially where high-dose brachytherapy equipment is used. Patients with concomitant medical conditions such as diabetes mellitus, collagen diseases and inflammatory bowel disease also may be at special risk. Previous surgery may predispose patients to radiation damage, especially where segments of bowel have been immobilized due to adhesions, or have a precarious blood supply. Following many pelvic cancer operations, small intestine prolapses into the void created by surgical resection, placing itself very close to the high-dose volume used in subsequent radiotherapy. Various surgical manoeuvres can reduce this problem by installing tailored omentum or artificial fabrics and meshes that serve to retain the bowel loops beyond the high-dose volume. Although well described,[4] and apparently of benefit, such techniques are used in a relatively small number of centres. Care in patient selection and meticulous attention to detail in planning both surgery and radiotherapy will reduce the incidence of serious complications to a minimum, typically to around 3% of patients treated with radical intent. Multiple field techniques and computed tomography (CT) planning can minimize unnecessary exposure of intestine to radiation.

It is of critical importance to avoid high dose per fraction regimens when irradiating the abdomen and pelvis.

Actual incidences of radiation enteritis are quoted between 5 and 15%, though in some series where high dose per fraction or high-dose brachytherapy has been used, higher figures are reported.

Late radiation enteritis is a much more serious and intractable form of bowel damage. Symptomatically, it is characterized by diarrhoea, frequency and chronic blood loss in the stool. In severe cases, atrophy of the glandular epithelium and microvascular damage become long-standing features, with eventual thickening of the bowel wall, malabsorption and loss of function leading to ileus. Contrast radiology may show localized segments of thickened bowel, with narrowing of the lumen, sometimes with evidence of fistula or perforation. Surgical intervention may be necessary in such cases, but is never easy because of adhesion formation, and the low viability of remaining loops of bowel. The options are usually to bypass the involved bowel, or to attempt a resection, and the choice of which procedure to undertake is best left to an experienced bowel surgeon.

Another effect of bowel irradiation is measurable long-term impairment of bowel function. The significance of this malabsorption in nutritional terms has almost certainly been underestimated in the past, and in frail patients it may be a significant health determinant. The existence of radiation-induced enteritis is usually defined by the presence of symptoms, but Yeoh *et al.*, in a series of studies,[5,6] have shown that measurable bowel dysfunction occurs as a persistent feature, often for years, following pelvic or abdominopelvic radiotherapy. These patients may have relatively minor symptoms, consisting of increased bowel frequency, yet they may have significant functional impairment in terms of malabsorption.[5,6] Since patients treated with curative intent are likely to have undergone such treatment, there may be hitherto unrecognized implications for their health as it inevitably deteriorates with increasing age.

Mechanisms of diarrhoea in cancer patients

Radiation and chemotherapy produce diarrhoea by decreasing fluid reabsorption and reducing transit time. These physiological features of diarrhoea are not cause-specific, and operate through a final common pathway of gut-regulatory peptides.[7] Accordingly, upregulation is possible by drugs that serve to modulate regulatory peptides,[8] with consequent reduction of symptoms and improvement of function.

Experimental models, mainly animal models, have been developed to investigate the physiology of treatment-related diarrhoea. Some of these involve surgically exposing a loop of bowel which is then irradiated extracorporeally.[3] These models have been used to evaluate a variety of possible treatments, which aim to limit damage to gut epithelium.[2,3,9]

Measurement of damage caused by both radiation and chemotherapy can be assessed by changes in gut morphology, counting of surviving crypts, measurement of DNA content and epithelial kinetic profiling.

Data from these model systems have been used to assess possible methods for protecting gut mucosa from radiation damage. Several agents appear to confer a degree of protection when delivered intraluminally. These include misoprostol, methylprednisolone, non-steroidal anti-inflammatory drugs (NSAID) and antioxidants.[2] Neutralization of bile salts and enzymes, and lumenal alkalinization also confer modest protection. None of these agents is yet established as an effective radioprotective in humans, however. One clinical study, designed to assess the effect of the active metabolite of sulphasalazine, yielded a negative

result, with exacerbation of symptoms in the treated group.[10]

Diarrhoea may also be causally associated with the presence of certain malignancies. These include medullary carcinoma of the thyroid,[11] 'vipomas' (vasoactive intestinal peptidomas) and pancreatic neoplasia.[12] Inappropriate production of peptides with gut-regulatory activity may also be a cause of symptoms. Autonomic disturbance is another potential cause, either because of drugs, malignant autonomic neuropathy, or following interventional procedures such as coeliac ganglion blockade,[13] or certain surgical procedures such as vagotomy and gastrectomy.[14]

Patients with suppressed immunity, either as a consequence of cancer treatment or an immune deficiency state such as AIDS, are especially susceptible to superadded infections which can cause serious diarrhoeal states.[15,16] *Clostridium difficile* has been reported to be a common cause in these patients, and may complicate cytotoxic chemotherapy.[17]

In patients undergoing transplantation, graft-versus-host disease can produce severe bowel damage and diarrhoea, which in severe cases can be life-threatening. Octreotide has proved to be of considerable value in the management of this complication.

Therapeutic uses of octreotide

Octreotide (Sandostatin, Sandoz) is a synthetic analogue of somatostatin, a physiological growth hormone release inhibitor which is extensively distributed throughout the gastrointestinal tract.

Somatostatin itself is thought to have a very short biological half-life, in keeping with its function as a short-range regulator. Several analogues have been synthesized, of which octreotide is the best established. It has a much longer duration of action than somatostatin, and is conventionally given by subcutaneous injection because of its very limited activity when given by the oral route. Also, rebound hypersecretion of hormone seems to be less of a problem with octreotide than with the parent molecule, somatostatin. Octreotide has been used in a variety of diarrhoeal states, including radiation enteritis, chemotherapy-induced diarrhoea, AIDS, graft-versus-host disease, endocrine diarrhoea, tumour-associated diarrhoea and diarrhoea associated with carcinoid malignancies.[8] The drug is well tolerated, and can be self-administered by subcutaneous injection. At an initial dose of 50 μg every 8 h, side effects are uncommon, although local irritation at the injection site, nausea, hyperglycaemia and hepatic dysfunction have all been reported. Relief of symptoms is generally prompt, but higher doses may be needed where symptoms persist or in patients with a large tumour burden. In addition to its considerable value as an agent for symptom relief, octreotide may also have some direct anti-tumour effects,[18–20] although these generally amount to sporadic partial responses. These effects are thought to be mediated by binding of octreotide and analogues to specific receptors which have been identified on tumours, and which have even allowed scintigraphic localization of tumour masses with suitably labelled material. These have been described in carcinoid malignancies, where the drug has been used in combination with interferon, and also in prostatic carcinoma.[20]

The mechanism underlying such effects is at present poorly understood. Further studies are needed to define any possible role for octreotide as an anti-tumour agent, either singly or in combination with other biological response modifiers such as interferon.

Graft-versus-host disease

Secretory diarrhoea is a prominent feature of graft-versus-host disease which can be life-threatening in transplant patients.[21] Stool output can be prodigious, often exceeding 3 litres/24 h.[21,22] and occasionally as high as 15 litres/24 h.[23] It has been proposed that the diarrhoea in these patients is multifactorial, resulting from mucosal damage, infection (bacterial or viral), hypersecretion and local cytokine release.[21] Treatment with octreotide generally results in prompt reduction of stool volume, but some patients in whom only a small improvement is obtained will respond to dose escalation. The typical octreotide dosage ranges from 50 μg three times a day to 600 μg three times a day, or more.[21,22] Some patients may fail to respond at all, which suggests that there is a lower limit to the amount of intact colonic epithelium necessary for a response to be obtained.[21] Early recognition of graft-versus-host disease is most important, and with the advent of octreotide there is now a very effective treatment for this potentially devastating feature of the disease.

Cytotoxic chemotherapy

Cytotoxic chemotherapy, particularly for gastrointestinal malignancies, may produce diarrhoea. Many combination regimens can produce a degree of diarrhoea, but notably those containing 5-fluorouracil and analogues, 5-fluorouracil + folinic acid in combination, methotrexate and cisplatin.[24,25] Mucosal damage, especially with 5-fluorouracil and methotrexate, may be associated with local or systemic infection. For patients taking cisplatin in moderate- or high-dose schedules, the incidence of diarrhoea appears to be at least 20%.[25] Treatment of drug-associated diarrhoea is important to reduce morbidity and promote compliance.

In a prospective randomized study of 43 patients, Cascinu *et al.*[24] have demonstrated a statistically significant benefit in favour of octreotide versus placebo. The authors also comment on the absence of adverse effects of octreotide treatment in their series. In a prospective study of 16 patients, Petrelli *et al.*[26] observed resolution of diarrhoea in 15 (94%). These authors also report an absence of adverse effects of treatment.

The superiority of octreotide over more conventional anti-diarrhoeal agents was also demonstrated by Gebbia *et al.*[27] in a series of 40 patients who were randomly allocated to treatment with either octreotide or loperamide. Of those treated with octreotide, 80% showed complete resolution of symptoms within 4 days versus 30% treated with loperamide ($P<0.001$). There was a similar highly significant advantage in favour of octreotide when the mean duration of treatment necessary to achieve remission was studied.

A review of patients treated with octreotide in our own unit during the last 2 years disclosed 19 patients, of whom 12 had carcinoid tumours, three had radiotherapy-related diarrhoea (radiation enteritis), three had diarrhoea as an acute result of radiotherapy and chemotherapy, and one had copious mucous discharge from a very extensive rectal carcinoma. Of those patients who were assessable, 12 had excellent or complete control of symptoms, including the patient with the discharging rectal tumour.

In two patients, there was minor benefit only and one patient was unable to tolerate octreotide. No objective tumour responses were seen, but a transient reduction (to <50% of pretreatment levels) of 5-hydroxyindoleacetic acid excretion was seen in four patients with carcinoid tumours.

Conclusions

Octreotide appears to have a major therapeutic effect in the management of diarrhoea related to cancer therapy, both in the acute diarrhoea following radiation therapy and chemotherapy and also in late radiation enteritis. Early treatment improves symptom control and can prevent potentially important morbidity in patients vulnerable to infection and fluid loss. Diarrhoea as a complication of AIDS, graft-versus-host disease and tumour-related diarrhoea can also be treated with octreotide. There is also a considerable body of work on the use of octreotide in related conditions.[28–43] This agent should therefore be considered for first-line treatment in patients for whom diarrhoea may be a serious complication.

References

1. Delaney JP, Bonsack ME, Felemovicius I. Misoprostol in the intestinal lumen protects against radiation injury of the mucosa of the small bowel. *Radiat Res* 1994; **137**: 405–409.
2. Delaney JP, Bonsack ME, Felemovicius I. Lumenal route for intestinal radioprotection. *Am J Surg* 1993; **166**: 492–501.
3. Fedorak RN, Allen SL. Effect of somatostatin analog (SMS 201-995) on *in vivo* intestinal fluid transport in rats: a limited systemic effect. *Dig Dis Sci* 1989; **34**: 567–572.
4. Lechner P, Cesnik H. Abdominopelvic omentopexy: preparatory procedure for radiotherapy in rectal cancer. *Dis Colon Rectum* 1992; **35**: 1157–1160.
5. Yeoh EK, Horowitz M, Russo A, *et al.* Gastrointestinal function in chronic radiation enteritis: effects of loperamide-N-oxide. *Gut* 1993; **34**: 476–482.
6. Yeoh E, Horowitz M, Russo A, *et al.* Effect of pelvic irradiation on gastrointestinal function: a prospective longitudinal study. *Am J Med* 1993; **95**: 397–406.
7. Shulkes A. Gastrointestinal hormones: from basic science to a clinical perspective. *Aust NZ J Surg* 1990; **60**: 575–578.
8. Battershill PE, Clissold SP. Octreotide: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in conditions associated with excessive peptide secretion. *Drugs* 1989; **3**: 658–702.
9. McKenna KJ, Ligato S, Kauffman GLJ, *et al.* Epidermal growth factor enhances intestinal mitotic activity and DNA content after acute abdominal radiation. *Surgery* 1994; **115**: 626–632.
10. Baughan CA, Canney PA, Buchanan RB, Pickering RM. A randomized trial to assess the efficacy of 5-aminosalicylic acid for the prevention of radiation enteritis. *Clin Oncol R Coll Radiol* 1993; **5**: 19–24.
11. Smid WM, Dullaart RP. Octreotide for medullary

thyroid carcinoma associated diarrhoea. *Neth J Med* 1992; **40**: 5–6.
12. Buchanan KD, Collins JS, Varghese A, *et al.* Sandostatin and the Belfast experience. *Digestion* 1990; **45** (suppl 1): 11–14.
13. Dean AP, Reed WD. Diarrhoea: an unrecognised hazard of coeliac plexus block. *Aust NZ J Med* 1991; **21**: 47–48.
14. Mackie CR, Jenkins SA, Hartley MN. Treatment of severe postvagotomy/postgastrectomy symptoms with the somatostatin analogue octreotide. *Br J Surg* 1991; **78**: 1338–1343.
15. Collignon A, Jeantils V, Cruaud P, *et al.* Prevalence of *Clostridium difficile* and toxin A in feces of HIV infected patients [in French]. *Pathol Biol Paris* 1993; **41**: 415–420.
16. Girard PM, Goldschmidt E, Vittecoq D, *et al.* Vapreotide, a somatostatin analogue, in cryptosporidiosis and other AIDS-related diarrhoeal diseases. *AIDS* 1992; **6**: 715–718.
17. Nielsen H, Daugaard G, Tvede M, *et al.* High prevalence of *Clostridium difficile* diarrhoea during intensive chemotherapy for disseminated germ cell cancer. *Br J Cancer* 1992; **66**: 666–667.
18. Fiasse R, Pauwels S, Rahier J, *et al.* Use of octreotide in the treatment of digestive neuroendocrine tumours: seven year experience in 20 cases including 9 cases of metastatic midgut carcinoid and 5 cases of metastatic gastrinoma. *Acta Gastroenterol Belg* 1993; **56**: 3–4.
19. Creutzfeldt W, Bartsch HH, Jacubaschke U, *et al.* Treatment of gastrointestinal endocrine tumours with interferon alpha and octreotide. *Acta Oncol* 1991; **30**: 529–535.
20. Verhelst J, De Longueville M, Ongena P, *et al.* Octreotide in advanced prostatic cancer relapsing under hormonal treatment. *Acta Urol Belg* 1994; **62**: 83–88.
21. Tenny CM, Przepiorka D, Shapiro S, *et al.* Octreotide for transplant related diarrhoea [abstract 1160]. *Proc Am Soc Clin Oncol* 1991; **10**: 329.
22. Bianco JA, Higano C, Singer J, *et al.* The somatostatin analog octreotide in the management of the secretory diarrhoea of the acute intestinal graft-versus-host disease in a patient after bone marrow transplantation. *Transplantation* 1990; **49**: 1194–1195.
23. Ely P, Dunitz J, Rogosheske J. Use of a somatostatin analog, octreotide acetate, in the management of acute gastrointestinal graft-versus-host disease. *Am J Med* 1991; **90**: 707–710.
24. Cascinu S, Fedeli A, Fedeli SL, *et al.* Control of chemotherapy-induced diarrhoea with octreotide in patients receiving 5-fluorouracil. *Eur J Cancer* 1992; **28**: 2–3.
25. Cascinu S, Fedeli A, Fedeli SL, *et al.* Control of chemotherapy-induced diarrhoea with octreotide. *Oncology* 1994; **51**: 70–73.
26. Petrelli NJ, Rodriguez-Bigas M, Rustum Y, *et al.* Bowel rest, intravenous hydration, and continuous high dose infusion of octreotide acetate for the treatment of chemotherapy-induced diarrhoea in patients with colorectal carcinoma. *Cancer* 1993; **72**: 1543–1546.
27. Gebbia V, Carreca I, Testa A, *et al.* Subcutaneous octreotide versus oral loperamide in the treatment of diarrhoea following chemotherapy. *Anti-Cancer Drugs* 1993; **4**: 443–445.
28. Bisset WM, Jenkins H, Booth I, Smith V, Milla PJ. The effect of somatostatin on small intestinal transport in intractable diarrhoea of infancy. *J Pediatr Gastroenterol Nutr* 1993; **17**: 169–175.
29. Burroughs AK, Malagelada R. Potential indications for octreotide in gastroenterology: summary of workshop. *Digestion* 1993; **54** (suppl 1): 59–67.
30. Linkesch M, Kuzmits R, Geyer G. Therapy of metastatic carcinoid with the somatostatin analog octreotide and with recombinant interferon alfa 2b. *Wien Klin Wochenschr* 1989; **101**: 455–457.
31. Mahler C, Verhelst J, De Longueville M, Harris A. Long-term treatment of metastatic medullary thyroid carcinoma with the somatostatin analogue octreotide. *Clin Endocrinol (Oxf)* 1990; **33**: 261–269.
32. Manfredi R, Vezzadini P, Costigliola P, Ricchi E, Fanti MP, Chiodo F. Elevated plasma levels of vasoactive intestinal peptide in AIDS patients with refractory idiopathic diarrhoea: effects of treatment with octreotide. *AIDS* 1993; **7**: 223–226.
33. Misra SC. Endocrine diarrhoeas; current concepts. *Trop Gastroenterol* 1990; **11**: 87–98.
34. Moroni M, Esposito R, Cernuschi M, Franzetti F, Carosi GP, Fiori GP. Treatment of AIDS-related refractory diarrhoea with octreotide. *Digestion* 1993; **54** (suppl 1): 30.
35. Mourad FH, Gorard D, Thillainayagam AV, Colin Jones D, Farthing MJ. Effective treatment of diabetic diarrhoea with somatostatin analogue, octreotide. *Gut* 1992; **33**: 1578–1580.
36. Neef B, Horing E, von Gaisberg U. Successful treatment of a life-threatening ileostomy diarrhea with the somatostatin analog octreotide. *Dtsch Med Wochenschr* 1994; **119**: 869–874.
37. Nightingale JM, Walker ER, Burnham WR, Farthing MJ, Lennard Jones JE. Octreotide (a somatostatin analogue) improves the quality of life in some patients with a short intestine. *Aliment Pharmacol Ther* 1989; **3**: 367–373.
38. Oberg K, Norheim I, Theodorsson E. Treatment of malignant midgut carcinoid tumours with a long-acting somatostatin analogue octreotide. *Acta Oncol* 1991; **30**: 503–507.
39. Parmar H, Charlton CD, Phillips RH, *et al.* Therapeutic response to somatostatin analogue, BIM 23014, in metastatic prostatic cancer. *Clin Exp Metastasis* 1992; **10**: 3–11.
40. Philippe J. APUDomas: acute complications and their medical management. *Baillieres Clin Endocrinol Metab* 1992; **6**: 217–228.
41. Romeu J, Miro JM, Sirera G, *et al.* Efficacy of octreotide in the management of chronic diarrhoea in AIDS. *AIDS* 1991; **5**: 1495–1499.
42. Verhelst J, De Longueville M, Ongena P, Denis L, Mahler C. Octreotide in advanced prostatic cancer relapsing under hormonal treatment. *Acta Urol Belg* 1994; **62**: 83–88.
43. Woods HF, Bax ND, Ainsworth I. Abdominal carcinoid tumours in Sheffield. *Digestion* 1990; **45** (suppl 1): 17–22.