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Palliation of Malignant Intestinal Obstruction Using Octreotide

David Khoo, Elizabeth Hall, Roger Motson, Julia Riley, Karen Denman and Jonathan Waxman

Vomiting due to malignant intestinal obstruction is an unpleasant terminal event in many cancer patients, which responds poorly to conventional therapies. Somatostatin and its long-acting analogues reduce intestinal secretion. For this reason, octreotide was used in a phase I/II study of patients with intractable vomiting secondary to intestinal obstruction due to malignant disease. Vomiting was controlled or the volume of nasogastric aspirate was markedly reduced in 18 of 24 (75%) patients receiving a subcutaneous infusion of octreotide (median initial dose 300, range 100–600 μg/day) for a median of 9.4 (range 1–38) days. A further 2 patients had partial relief of their symptoms. Octreotide is an effective treatment of nausea and vomiting due to malignant bowel obstruction.
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INTRODUCTION

INTESTINAL OBSTRUCTION is a frequent terminal event in many malignancies, commonly complicating ovarian and gastrointestinal tumours. The symptoms of this condition are unpleasant and include abdominal pain, vomiting and constipation. Surgery may relieve this condition, but is not usually warranted in view of the limited prognosis. Conservative management, by nasogastric intubation or with anti-emetics and high dosage steroids, is frequently ineffective and generally suboptimal, leading to an extremely poor quality of the patient's remaining life [1].

Somatostatin has a wide range of endocrine effects, amongst which are the reduction in intestinal secretion and suppression of the release of gut peptide hormones [2]. It has a short half life, and because of this, long-acting analogues such as octreotide were designed with similar endocrine effects to the native hormone. These have been effective in a number of endocrine conditions and in malignant disease [2].

In experimental models, somatostatin stimulates intestinal lumenal sodium, chloride and water absorption [3], and reduces ileal distention in small bowel obstruction [4]. Octreotide has similar effects, and has been successfully used in the treatment of small bowel fistula [5, 6].

These observations of the effects of somatostatin analogues on intestinal secretion have led us to investigate the use of octreotide to palliate the symptoms of intestinal obstruction in terminally ill patients with malignant disease.

Correspondence to J. Waxman.
D. Khoo, R. Motson and K. Denman are at the Colchester General Hospital, Colchester CO4 5JL; E. Hall is at the St Helena Hospice, Colchester CO4 4JU; J. Riley is at the Princess Alice Hospice, West End Lane, Esher, Surrey; and J. Waxman is at the Department of Clinical Oncology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, U.K.
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PATIENTS AND METHODS

Patients

All consecutive patients presenting to our units between February 1991 and October 1992 with intestinal obstruction due to malignancy were considered for treatment with octreotide. Patients whose life expectancy exceeded 2 months were managed surgically, and all terminally ill patients with a shorter life expectancy (Karnofsky score $< 50\%$) were treated medically. 24 patients received octreotide therapy. 21 had had abdominal surgery at their initial presentation, and of these, 8 also had a second laparatomy for obstruction. The diagnosis of intestinal obstruction was made on the basis of clinical symptoms of vomiting, constipation, abdominal pain, signs of abdominal distension and obstructive bowel sounds. Patients without these signs were excluded from the study, as were patients with other causes for nausea, such as ascites or metabolic disorders. Radiological evidence of intestinal obstruction was obtained in 17 patients. All patients had WHO grade 4 vomiting and had failed prior treatment with a combination of anti-emetics, steroids and/or naso-gastric drainage for a period of at least 24 h. Further details of the patients are provided in Table 1.

Treatment and assessment of response

All patients were initially treated in hospital or in a hospice. The number of times each patient vomited, together with the volume of nasogastric aspirate, were charted by the nursing staff. Each patient was asked whether they had experienced nausea during the previous 24 h, and this was recorded by the nursing staff. Treatment with octreotide was started at a dose of 50 μg, three times a day, subcutaneously, according to the manufacturer's data sheet recommendations, and increased by 50 μg increments until control of vomiting was achieved for a minimum of 24 h. This regimen was followed for the first 2 patients entered into this study. Subsequently, to avoid repeated injections, octreotide was given by continuous subcutaneous

Table 1. Patients' details

Age (years)	Primary tumour	Pretreatment emesis (days)	Octreotide Initial dose	Octreotide Final dose	Treatment (days)	Response (WHO grade)
70	Ovary	10	300	300	1	0
84	Stomach	3	300	150	14	0
71	Gall bladder	21	300	150	9	0
83	Colorectal	14	300	150	23	0
61	Stomach	35	150	150	3	0
81	Colorectal	6	150	150	21	0
88	Duodenum	10	300	150	7	0
68	Ovary	90	150	200	9	2
53	Pancreas	3	100	200	38	0
73	Colorectal	3	600	300	3	2
66	Ovary	7	300	300	4	0
76	Liver (cholangiocarcinoma)	17	100	300	16	0
38	Cervix	5	300	450	7	0
65	Ovary	60	300	500	7	0
72	Colorectal	30	500	400	3	0
44	Appendix	7	100	600	11	1
58	Colorectal	2	600	600	10	0
55	Ovary	7	600	700	15	1
76	Ovary	3	300	300	1	3
79	Ovary	7	300	600	8	3
77	Colorectal	55	300	300	3	4
76	Pancreas	7	300	600	3	3
75	Colorectal	7	300	600	12	3
56	Colon	14	300	1200	3	4

Response: WHO emesis scale. 0, no vomiting; 1, nausea; 2, transient vomiting; 3, vomiting requiring therapy; 4, intractable vomiting.

infusion in either the upper arm or anterior chest wall using a portable syringe driver. These patients started treatment at a minimum dosage of 100 μg of octreotdie subcutaneously by continuous infusion, which was increased by 150 μg daily until control of vomiting was achieved. During treatment with octreotide, patients were on free fluids orally.

Patients were assessed for response using the WHO recommended scale; grade 0 is defined as no nausea and vomiting, grade 1 as nausea, grade 2 as transient vomiting, grade 3 as vomiting requiring therapy, and grade 4 as intractable vomiting. A complete response was when the WHO grade was reduced to 0 and a partial response if the grade was reduced to 2 or 1. 5 patients had nasogastric tubes in place, and in these patients, a reduction in the volume of effluent in 48 h to below one third of the level during the previous 48 h was recorded as a response (Fig. 1).

RESULTS

14 of 24 patients treated with octreotide had a complete response, and 4 patients a partial response, as shown in Table 1. This response was maintained to death in 16 patients. The median duration of vomiting prior to instituting treatment was 7.5 days (range 1–90). The median duration of treatment was 9.4 days (range 1–38). The control of vomiting was generally rapid, occurring within 2–4 h of achieving the correct total daily dosage of octreotide. The median initial dosage to control vomiting in responding patients was 300 μg/day (range 100–600). In 6 responding patients, treatment was reduced by 50 μg increments daily from a median dosage of 300 μg/day (range 300–600) to a final dosage of 150 μg/day (range 150–300) without loss of response. In 8 of the responding patients, the final treatment dosage was increased from 125 μg (range 100–600) to a median of 300 μg (range 200–700) daily. In the remaining 5 responding patients, the dosage was not changed. Figure 1 illustrates the reduction of nasogastric aspirate in all 5 patients who had nasogastric tubes. 7 patients did not respond, despite dosages of between 600 and 1200 μg/24 h of octreotide. There was absolutely no toxicity related to octreotide treatment.

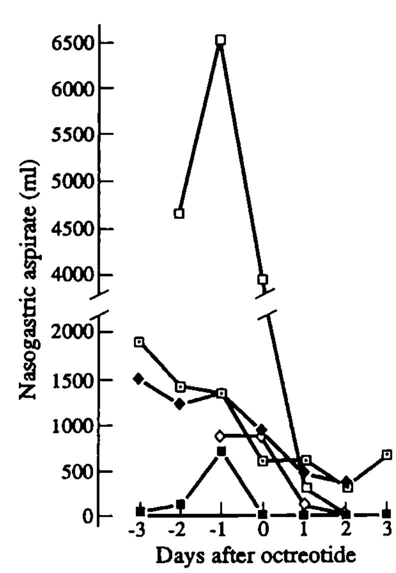

Fig. 1. Nasogastric aspirate of obstructed patients during treatment with octreotide. Each line represents 1 patient.

DISCUSSION

The symptoms of intestinal obstruction in advanced malignancy are amongst the most distressing experienced by terminally ill patients, complicating 10% of hospice admissions [1]. In such patients, surgery offers the best chance for a sustained relief of symptoms, but is impractical where there is a limited outlook. In this situation, medical therapies are ineffective. Many of the conventional treatments for intestinal obstruction have side-effects. High dosage anti-emetics may have extrapyramidal toxicities, steroids have a plethora of side-effects and nasogastric tubes are uncomfortable. However, octreotide has no significant toxicity [2]. In this present study, 18/24 consecutive patients responded to octreotide given for intestinal obstruction due to a wide variety of different intra-abdominal malignancies. This high response rate is very encouraging, and almost certainly relates to the known effect of somatostatin and its analogues in reducing gastrointestinal secretion. It was apparent that if a response was not obtained with a dose of octreotide of up to 600 μg/day by subcutaneous infusion, further symptomatic improvement would not be obtained with a higher dosage, and should not be tried. Other authors have described transient discomfort at the site of injection of octreotide, but this was not reported by our patients. The efficacy and lack of toxicity of octreotide confirm our earlier findings [7], and suggest that it is a valuable addition to the palliative care armamentarium, and provides an impetus for a phase III investigation.

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Second-line Treatment with Ifosfamide and Carboplatin in Patients with Ovarian Carcinoma Relapsing After Treatment with Carboplatin

Stephen P. Dobbs, Claire Gribbin, Stephen Y. Chan and Eric M. Bessell

20 patients with ovarian carcinoma whose disease had relapsed (1–42 months, median 4 months) after showing either response or stable disease to carboplatin, were treated with ifosfamide (5 g/m^2 intravenously over 24 h, day 1) and carboplatin (200 mg/m^2 intravenously day 2) as second-line treatment. The mean number of treatment cycles was 3.5 (range 1–6). The major toxicities were thrombocytopenia (WHO grade 3/4, 25%), neutropenia (WHO grade 3/4, 40%) and encephalopathy (WHO grade 3/4, 15%). Overall response rate was 15% [complete response, 0; partial response, 3 (15%); no change, 5 (25%) and progressive disease, 12 (60%)]. The median survival from the date of second-line treatment was 7 months. This combination offers no advantage over either agent used alone.

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INTRODUCTION

IFOSFAMIDE [1, 2] AND carboplatin [3, 4] have both been shown to have activity in ovarian carcinoma relapsing after cisplatin therapy. Markman and Hoskins [5] have recently stressed the importance of analysing separately those patients with primary platinum-resistant ovarian carcinoma from those with potentially platinum-sensitive disease when investigating the activity of regimes in relapsed ovarian carcinoma. Primary platinum-resistant disease is defined as disease only showing less than partial response to first-line platinum therapy. Potentially, platinum-sensitive disease is disease showing at least a partial response and can be sub-divided into platinum-free intervals of less than 6 months, 6–12 months, and greater than 12 months

Correspondence to E.M. Bessell.
The authors are at the Department of Clinical Oncology, City Hospital, Hucknall Road, Nottingham NG5 1PB, U.K.
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