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# Octreotide therapy in carcinoid disease

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**Octreotide therapy is expensive, but at present it and other somatostatin analogues appear to offer the best opportunity of controlling the symptoms of flushing and diarrhoea. It may also have other properties affecting general well-being. The question of whether it changes tumour growth remains unanswered and there is no convincing evidence that it alters survival. In all published studies the numbers of patients are small and there have been no control groups. However, since no other drug has yet proved effective against flushing, the somatostatin analogues, including octreotide, remain the treatment of choice for the symptomatic control of the carcinoid syndrome. Octreotide is of great therapeutic value pre-operatively and intra-operatively and it is essential that all operating theatres have this drug available for immediate use. Surgical debulking, if feasible, provides the best outcome potential in carcinoid disease. Present evidence suggests that the place of octreotide and other somatostatin analogues is in controlling the symptoms of the disease rather than its progress and in ensuring cardiovascular and respiratory stability during surgical procedures.**

*Key words:* Octreotide, carcinoid disease.

## Introduction

Carcinoid disease is not usually diagnosed until metastases are present.[1–3] In a series of 52 cases from Northern Ireland none was diagnosed pre-operatively.[2] We have had a similar experience in Sheffield with 116 cases of abdominal carcinoid tumour seen during the last 12 years.[3]

However, an early diagnosis will increase the likelihood of surgical treatment being of therapeutic value, and as yet no other therapy has been found to prolong life in patients with carcinoid disease. Moertel (1987)[4] showed that the 10-year survival of patients with an inoperable abdominal carcinoid tumour was 40%. This increased to 60% in patients with operable disease. Wangberg *et al.*[5] also found that survival figures were better in patients with operable disease. In their series of 48 patients, all with hepatic metastases, 11 were considered suitable for surgery and were alive with no evidence of tumour recurrence 3 months after starting therapy. Thus the importance of early diagnosis and surgical treatment is paramount. Octreotide and other somatostatin analogues are most useful in controlling the symptoms of the disease rather than its progress and in ensuring cardiovascular and respiratory stability during surgical procedures.

## Discovery of somatostatin analogues for treatment of carcinoid flushing

By the time most patients are diagnosed they will be experiencing episodes of diarrhoea or flushing or both of these symptoms. Previously, drugs such as diphenoxylate, cyproheptadine, methysergide and opium alkaloids were recommended for treatment of the diarrhoea and prochlorperazine, chlorpromazine, methyldopa and prednisone for treatment of the flushing.[6] There were no substantive data to support the use of these drugs, the recommendation for their use being based mainly upon anecdote or the treatment of very small numbers of patients.

A few years after Sjoerdsma's (1971)[6] recommendations a serendipitous discovery led to the use of somatostatin analogues in the treatment of symptoms of carcinoid disease. Frolich *et al.*[7] had learned of two patients with medullary carcinoma of the thyroid gland who flushed when treated with pentagastrin. These authors postulated that gastrin might be the cause of the carcinoid flush. Somatostatin had been previously shown to inhibit the release and action of gastrin,[8,9] and Frolich *et al.*[7] found that when given as an intravenous infusion to two patients with carcinoid disease it abolished the flushing induced by pentagastrin.

In 1981, Long *et al.*[10] reported the effects of intravenous somatostatin infusions on flushing in five patients with carcinoid disease. In common with Frolich *et al.*[7] they gave pentagastrin to provoke flushing, but flushing occurred in only two

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of the five. Somatostatin prevented the pentagastrin-induced flushing in these two patients and also preventing the flushing induced by intravenous noradrenaline in four of the patients. In addition to questioning the possibility that gastrin caused the carcinoid flush, Long *et al.* (1981)[10] demonstrated the protean inhibitory effects upon gut peptides of somatostatin. They observed decreases in plasma concentrations of gastrin, vasoactive intestinal peptide, neurotensin, pancreatic polypeptide, motilin, insulin, gastric inhibitory peptide, glucagon and enteroglucagon. At that stage it was unclear what peptide, if any, was responsible for the flushing. In one patient Long *et al.*[10] subcutaneously administered a nonapeptide analogue of somatostatin with D- rather than L-tryptophan in position 8 of the molecule. This compound caused a loss of flushing lasting 6–9 h.

## Development of octreotide

Neither Frolich *et al.*[7] nor Long *et al.*[10] mentioned the beneficial effect of somatostatin on diarrhoea which had been described the year before by Davis *et al.*[11] and Dharmsathaphorn *et al.*[12]

The short duration of action of a single bolus dose of somatostatin was a major constraint in its clinical use. Painstaking synthetic chemistry resulted in the production of octreotide, an octapeptide analogue of somatostatin.[13] Octreotide was found to have far more favourable pharmacokinetics than somatostatin, with a corresponding increase in the duration of its biological effect.[14]

In the mid-1980s many reports appeared about the effect of octreotide in patients with carcinoid disease. The incidence of carcinoid disease is such that these reports were of small numbers of patients or simply case reports. Nevertheless, there was an evolving consensus that octreotide was able to palliate the symptoms of the disease or, to be more precise, the symptoms of the syndrome.[15–19]

## Effects of octreotide on diarrhoea and flushing: clinical studies

The first large study demonstrating the symptomatic benefit afforded by octreotide was reported by Kvols and his colleagues in 1986.[20] Most patients treated showed an improvement in the symptoms of flushing and diarrhoea and a decrease in the urinary output of 5-hydroxyindole acetic acid (5-HIAA). These findings have been replicated in a number of other studies (Table 1). There is no doubt that octreotide gives considerable symptomatic benefit but there is no firm evidence that it causes regression of tumours, either primary or secondary. A number of studies have suggested that octreotide therapy might result in tumour regression (Table 1) but the numbers of patients involved were small and none of the studies had a control treatment arm.

Table 1 shows data from the larger octreotide studies conducted over the last 10 years which included the greatest amount of clinical data. Not all patients were previously untreated and in the five studies for which data were given, 70 out of 135 patients (51%) had undergone previous chemotherapy. There was little information about previous surgery, embolization or concurrent therapy. The 1993 study by Anthony *et al.*[25] was different from the others in that the octreotide dose was increased stepwise at 6-week intervals, from 450 to 6000 μg/day (Figure 1). The greatest fall in mean 5-HIAA excretion was seen with 450 μg octreotide per day and with both time and an increase in the dose the mean 5-HIAA excretion rose. This might have been due to disease progression or to tachyphylaxis. Others have observed a diminishing effect of octreotide with time (Table 1), but whether this is solely the result of tachyphylaxis has never been determined.

Octreotide is effective in decreasing the frequency of flushing and diarrhoea, and data from our own patients are shown in Figures 2 and 3. Octreotide also increases the performance status of patients as measured on the Karnofsky scale,[25] the improvement being seen within a month of starting treatment.

We have observed a rapid improvement in two other clinical features of carcinoid disease, namely 'depression' and loss of appetite in response to octreotide therapy.[3] Neither of these two symptoms was evaluated prospectively and for this reason the diagnosis of depression is in doubt. Shortly after the beginning of treatment these two symptoms were resolved in some patients. It was thought, retrospectively, that 14 (76%) in a group of 19 patients were depressed before starting octreotide treatment. Within 4–6 weeks, at the time of the lowest urinary 5-HIAA excretion and with octreotide doses ranging from 100 to 200 μg three times a day, only two (11%) patients remained depressed. Three to six months later approximately half of the patients were depressed again. Within the first week of starting octreotide therapy 15 (79%) patients reported an increase in their appetite.

**Table 1.** Results of clinical studies on octreotide

| | Kvols *et al.* (1986)[20] | Kvols *et al.* (1987)[21] | Vinik and Moattari (1987)[22] | Oberg *et al.* (1991)[23] | Janson and Oberg (1993)[24] | Anthony *et al.* (1993)[25] | Sheffield (unpublished data) |
|---|---|---|---|---|---|---|---|
| *n* | 25 | 28 | 14 | 23 | 55 | 14 | 18 |
| Previous treatment | | | | | | | |
| Chemotherapy | 15 | NS | 5 | 16 | 39 | NS | 0 |
| Hepatic resection | NS | NS | 3 | NS | NS | NS | 0 |
| Embolization | NS | NS | 0 | 0 | NS | NS | 0 |
| Concurrent treatment | NS | NS | NS | NS | NS | 5-FU | CP CH |
| Octreotide (mg/day) | 450 | 1500 | 200–1000 | 200 | 100–1200 | 1500–6000 | 450–1500 |
| Favourable effects | | | | | | | |
| Decreased flushing | 24 | 24/25 | 9/9 | 11/22[a] | 32/46 | NS | 14/15 |
| Decreased diarrhoea | 22 | 220/24 | 10/12 | 11/22[a] | 31/45 | NS | 10/14 |
| Decreased 5-HIAA | 24 | 28 | 6/8 | NS | 16/43 | NS | 17/18 |
| Decreased tumour size | ND | 4/23 | NS | NS | 1 | 4/13[b] | 0 |
| Adverse effects | | | | | | | |
| Steatorrhoea | 8/12 | Yes (?)[c] | Yes[c] | – | – | Yes[c] | 18/18[d] |
| Hyperglycaemia | 2/25 | – | – | 8/22 | – | 3/14 | – |
| Injection site pain | – | – | Yes | – | – | – | 18/18 |
| Gallstone | – | 1/28 + biliary sludge | 1/14 | – | 4/55 | – | 1/18 |
| Diarrhoea | – | – | – | 10/22 | Yes | – | 1 |
| Cholangitis | – | – | – | 1/23 | – | – | – |
| Symptom recurrence | Yes | NS | NS | NS | Yes | NS | Yes |

CP, codeine phosphate; CH, cyproheptadine; 5-FU, 5-fluorouracil (one patient only); 5-HIAA, 5-hydroxyindole acetic acid; NS, not stated; ND, not determined.
[a]Decrease in flushing and/or diarrhoea.
[b]Partial response only.
[c]Numbers not stated.
[d]Smelly motions.

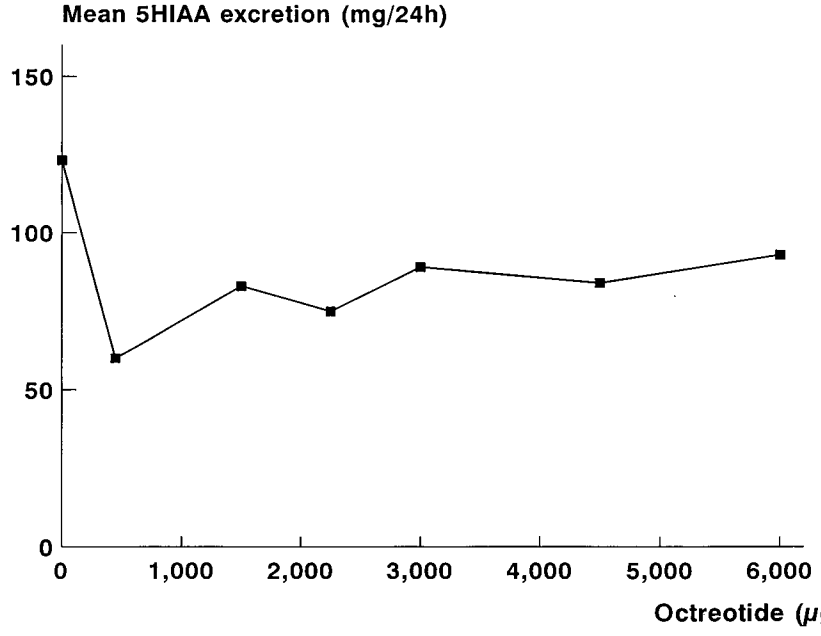


**Figure 1.** Effect of increasing the daily octreotide dose on urinary 5-hydroxyindole acetic acid (5HIAA) excretion in 14 patients with carcinoid disease. The dose was increased every 6 weeks. SEM, 20–50%. Data from Anthony *et al.*[25]

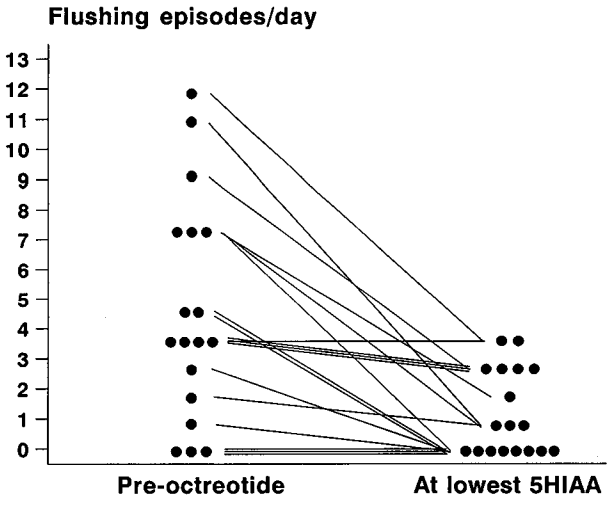


**Figure 2.** Effect of octreotide therapy (100–200 mg three times a day) on the frequency of flushing attacks in 18 patients with carcinoid disease, all of whom had hepatic secondary deposits. 5HIAA, 5-hydroxyindole acetic acid.

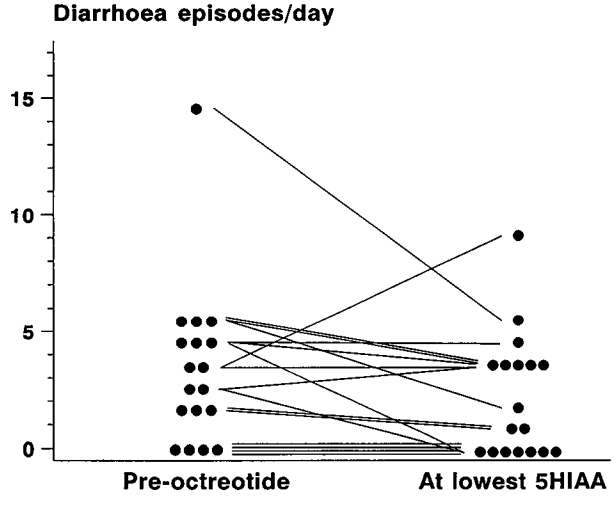


**Figure 3.** Effect of octreotide therapy (100–200 mg three times a day) on the frequency of diarrhoea in 18 patients with carcinoid disease, all of whom had hepatic secondary deposits. 5HIAA, 5-hydroxyindole acetic acid.

## Effects of octreotide on tumour size

One major difficulty in studying carcinoid disease is its rarity. It is unlikely that any one group will see sufficient patients to allow them to study the efficacy of various drug treatments. This was a problem with many of the early chemotherapy studies and remains a problem with the largest recent octreotide studies (Table 1). In one of the larger studies of chemotherapy,[26] tumour mass and its shrinkage in response to treatment was assessed by palpation of the abdomen. In that study, although some livers shrank in response to streptozotocin plus either 5-fluorouracil or cyclophosphamide, there was no good evidence that chemotherapy shrank the hepatic secondary deposits. Similar results have been obtained with octreotide therapy. Despite an occasional patient showing some tumour shrinkage (Table 1) there is no convincing evidence, as yet, that octreotide causes tumour regression. Furthermore, combination therapy with octreotide and interferon-α did not result in a significant reduction of tumour mass.[27]

A large study from Germany [28] examined the effects of octreotide therapy in 115 patients with gastroenteropancreatic tumours, 53 with the carcinoid syndrome and 45 with 'non-functioning tumours'. Tumour size was estimated by abdominal computed tomography in 68 of these patients at least 3 months and up to 12 months after starting treatment. The data presented do not show the effect of octreotide in the carcinoid patients specifically, but overall, a partial regression of tumours (defined as a decrease of >25% in tumour size) was seen in three patients. The tumour size was said to be stable (<25% increase or decrease in tumour size) in 34 patients, but the short follow-up and slow-growing nature of the tumours may have precluded the detection of any changes, and as with other studies there was no control group.

## Adverse effects of octreotide

The adverse effects of octreotide are difficult to assess in a quantitative way from the published studies, because the data presented do not always include the number of patients affected. Steatorrhoea, possibly secondary to the effect of octreotide on cholecystokinin release, is common and this may explain why the drug appears to have a greater effect on flushing than diarrhoea (Figures 2 and 3).

## Assessing efficacy

A major question is how best to measure the effectiveness of treatment with octreotide, or indeed any drug therapy used in the treatment of carcinoid disease. Patients want to know whether they will live a longer, better quality, life. While octreotide will give a better quality of life there is unfortunately no convincing evidence that it prolongs life. The

effect of octreotide on survival has never been studied formally. The measures of changes in urinary 5-HIAA excretion or other biochemical estimates do not appear to be correlated with survival. Possibly, the use of positron emission tomography may detect clinically useful metabolic changes in carcinoid tumours in response to therapy.[29]

Measurement of the urinary excretion of 5-HIAA is unhelpful in predicting which patients might experience intra-operative cardiovascular problems.[30] Patients with only modest elevations in urinary 5-HIAA excretion were just as likely to have disturbances in arterial blood pressure or the heart rate during an operation as those with marked elevations. Cardiovascular stability, an absence of bronchospasm and only rare episodes of flushing were seen in patients given pre-operative subcutaneous octreotide at 50–500 μg every 8 h (depending on the previous dose), or 50–100 μg every 8 h if not treated previously.[30] Further doses of octreotide (10–20 μg intravenously) might be given intra-operatively as required. Other groups have also found that octreotide therapy results in a stable anaesthetic induction and intra-operative period.[31–33]

It is unusual for octreotide not to have a beneficial effect on the symptoms of the carcinoid syndrome. In one group of 24 patients treated with octreotide at 100–1000 μg/day who had either not responded or who had responded initially and then redeveloped symptoms, the introduction of interferon-α resulted in a fall of over 50% in urinary 5-HIAA excretion in 17 out of 22 patients.[34] The significance of this observation is a little obscure since nine of these patients had been treated previously with interferon-α but had withdrawn from treatment either due to tumour progression or to toxicity.

## Conclusions

Octreotide therapy is expensive, but since no other class of drugs has so far proved effective in carcinoid disease, it and other somatostatin analogues appear to offer the best opportunity of controlling the symptoms of flushing and diarrhoea. Octreotide may also have other properties affecting general well-being. The question of whether it changes tumour growth remains unanswered and there is no convincing evidence that it alters survival. In all studies the numbers of patients are small and there are no control groups.

There have been no comparative studies between octreotide and other therapies which might control the diarrhoea seen in carcinoid disease, and such studies are now needed. At present no other drug has proved effective against flushing so the somatostatin analogues, including octreotide, remain the treatment of choice for the symptomatic control of the carcinoid syndrome.

Moreover, octreotide is of great therapeutic value both pre-operatively and intra-operatively and it is essential that all operating theatres have octreotide available for immediate use. It has been suggested that when a carcinoid tumour becomes insensitive to the effects of octreotide, surgical debulking, embolization and chemotherapy should be considered.[35] This suggestion was made some years ago, however, and the evidence now is that surgical debulking, if feasible, provides the best outcome potential.[35]

Present evidence thus suggests that the place of octreotide and other somatostatin analogues is in controlling the symptoms of the disease rather than its progress and in ensuring cardiovascular and respiratory stability during surgical procedures.

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