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The use of octreotide in the symptomatic treatment of patients with neuroendocrine tumours: a single-centre experience

Abstract

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours originating from endocrine cells scattered throughout the body and which form the diffuse endocrine system. Functioning tumours produce hormones or catecholamines which are responsible for the characteristic clinical picture.

Surgery is the treatment of choice for patients with NETs, although it can rarely be radical. Somatostatin analogues play an important role in the drug treatment of NETs, as they effectively control the signs and symptoms of the excessive release of hormones by these tumours. Treatment with somatostatin analogues improves the quality of life for the patient and prolongs survival.

We report on four patients with neuroendocrine tumours managed with somatostatin analogues: one male patient with carcinoid syndrome; one female patient with clinical manifestations of functioning VIPoma; and two male patients with ectopic ACTH syndrome.

Key words: somatostatin analogues, octreotide, neuroendocrine tumours

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Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours originating from the endocrine cells scattered throughout the human body and which form the diffuse endocrine system [1]. These tumours are rare and in most cases slow-growing, small and malignant. They may be hormonally active (functioning tumours) or not (non-functioning tumours). Functioning tumours produce hormones or catecholamines responsible for the characteristic clinical picture. Carcinoids account for the majority of NETs (approximately 50%) [1, 2]. The detectability of NETs is growing due to the increasing availability of modern diagnostic methods [1, 3].

Surgery is the treatment of choice for patients with NETs, including those with liver metastases. However, in the majority of cases, because of ad-

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vanced disease, a complete resection of the tumour is not possible [4, 5]. In patients who are not eligible for surgery, treatment is focused on improving the quality of life. Such treatment includes somatostatin analogues as first-line drugs and in some cases interferon-α, radionuclide therapy or chemotherapy [4, 6].

Somatostatin analogues, especially those with long-acting formulations, play a fundamental role in the pharmacological treatment of NETs [4, 7]. Somatostatin analogues are considered the "gold standard" in patients with neuroendocrine tumours and manifestations of hormonal hypersecretion [8].

Aim

The aim of the paper is to present the outcomes of octreotide treatment in four patients: one male patient with carcinoid syndrome; one female patient with the clinical manifestations of a tumour secreting vasoactive intestinal peptide (VIPoma); and two male patients with ectopic ACTH syndrome. They were hospitalized in the Department of Endocrinology and Diabetology, Medical College, Nicolaus Copernicus University, Bydgoszcz, Poland, between 2001 and 2006.

Case 1 — a patient with carcinoid syndrome

In 1997 a 43-year-old male patient (TG) developed the first manifestations of carcinoid syndrome: flushing and diarrhoea. A CT scan revealed two lesions in the liver suggestive of metastatic foci and holography demonstrated a tumour in the caecum. The diagnosis of carcinoid syndrome was confirmed by the 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) value of 775.4 μmol/g of creatinine (normal values $\leq$ 23 μmol/g of creatinine). A right hemicolectomy was performed and a histopathological examination of the resected material revealed a carcinoid tumour. After the surgery the patient was managed with a prolonged-release somatostatin analogue (lanreotide PR at the dose of 30 mg IM q4w), which reduced the number of flushing episodes and loose stools. No new liver laesions were revealed in imaging studies (CT, somatostatin receptor scintigraphy using OctreoScan). In September 1999 the patient discontinued treatment at the Endocrinology Clinic and stopped receiving any somatostatin analogue. In May 2001 the patient presented to the Outpatient Clinic of the Endocrinology Department of the University Hospital of the Medical College, Nicolaus Copernicus University, Bydgoszcz, Poland, with considerably exacerbated symptoms of carcinoid syndrome (flushing, diarrhoea, weight loss and asthaenia).

It was decided to make an attempt at resecting the metastatic foci of the carcinoid tumour visualized in the somatostatin receptor scintigraphy using OctreoScan as two foci in the right lobe of the liver. During the laparotomy, however, numerous carcinoid metastases were discovered and the decision to close the patient was made. At that time the patient was also diagnosed with chronic renal failure most likely caused by retroperitoneal fibrosis and tricuspid insufficiency with right-sided heart failure. In August 2001 the patient was started on octreotide 0.1 mg SC tid for 2 weeks, followed by a long-acting release (LAR) formulation at the dose of 10 mg IM q4w for one year. During the treatment we observed considerable improvement in his well-being and exercise tolerance, the number of flushing episodes decreased from 10 15 to 2 per day and the number of stools from 8 to 3 per day. The 24-hour urinary 5-HIAA excretion also decreased from 130 mg/day in August 2001 to 80 mg/day in March 2002. Between August 2002 and February 2003 the patient was not receiving the drug because the National Health Fund refused to reimburse the cost of it. As octreotide could not be continued, the use of ^{131}I metaiodobenzylguanidine (^{131}I-MIBG) was considered. However, due to the risk of the exacerbation of renal failure the patient was not found eligible for radionuclide therapy. In February 2003 the patient was started on LAR octreotide at the dose of 20 mg q1m, followed by 30 mg q1m during hospitalization at our Department of Endocrinology and Diabetology. While the treatment improved the patient's well-being, signs and symptoms of carcinoid syndrome and urinary 5-HIAA excretion, we observed progressive cachexia, deterioration in renal function and exacerbation of heart failure symptoms. The patient passed away in August 2004.

Case 2 — a patient with clinical manifestations of VIPoma

In 2000 a 28-year-old female (JM) developed abdominal pain and diarrhoea. The patient was passing up to 30 watery stools a day and had hypokaliaemia. In order to establish the cause of these symptoms, investigations for infectious diseases, food allergies, Crohn's disease and ulcerative colitis were performed. An upper GI endoscopy revealed multi-

ple oesophageal ulcerations, which healed following several months of proton pump inhibitor treatment. Abdominal ultrasound, upper and lower GI series and a flexible sigmoidoscopy showed no abnormalities. The diarrhoea persisted for two years and led to emaciation in the patient. In 2002, endoscopic ultrasound revealed an 8 mm lesion in the head of the pancreas. The somatostatin receptor scintigraphy using ^{11}In-OctreoScan revealed no signs of pathological focal tracer accumulation in the abdominal cavity. Gastrin levels were normal. The patient was started on short-acting octreotide, which resulted in clinical improvement and resolution of the symptoms. Treatment was continued with a LAR formulation at the dose of 20 mg IM q29d. In May 2003 the patient underwent a fine-needle aspiration biopsy of the hypoechoic lesion in the head of the pancreas detected sonographically. The aspirate contained non-characteristic proteinaceous content. Abdominal spiral CT and endoscopic retrograde cholangiopancreatography (ERCP) did not confirm the presence of the pancreatic tumour and no abnormalities were revealed by colonoscopy or by mesenteric and coeliac arteriography. The 24-hour urinary 5-HIAA excretion was normal. The positron emission tomography (PET) scan performed in October 2003 revealed no pathologies. Chromogranin A levels determined during octreotide treatment were in the range of the upper limit of normality (19.4 U/l).

In 2004 the frequency of LAR octreotide dosing was increased to 20 mg twice a month, as the symptoms had been worsening, achieving a considerable improvement of the patient's condition.

The somatostatin receptor scintigraphy using ^{99}Tc-HYNIC-Tyr^3-octreotide (^{99}Tc-HYNIC-TOC) performed in 2005 revealed pathological uptake of the tracer in the head of the pancreas. CT and MRI scans of the abdominal cavity and coeliac arteriography did not confirm the presence of any focal lesion in the pancreas. In spite of this, the patient was qualified for surgical tumour resection in July 2006.

During surgery the patient underwent scintigraphy, endoscopy of the stomach and duodenum and an ultrasound scan, all of which revealed no pathologies within the abdominal cavity. Lymph nodes surrounding the common hepatic artery were collected for intraoperative histopathology, which showed no malignant infiltration. In view of the above a decision not to proceed with the resection of the head of the pancreas was made.

The patient continues to be treated with LAR octreotide 20 mg q14d and passes approximately 3 formed stools a day. Periodically, she experiences exacerbations of diarrhoea and hypokaliaemia which require intravenous potassium supplementation. The patient's condition is good and the periodic exacerbations do not interfere with her daily activities; the patient remains in active employment.

Case 3 — a patient with ectopic ACTH syndrome in the course of thymic carcinoma

In 1995 a 31-year-old male (JB) developed gradually increasing asthenia, atrophy of the limb muscles, round face, striae, back pain and hypokaliaemia. In 1996, based on a clinical picture of high serum cortisol and abolition of the circadian variation in cortisol levels (627 ng/ml at 8:00 am and 625 ng/ml at midnight), a diagnosis of Cushing's syndrome was made. Very high ACTH levels (888 pg/ml at 8:00 am and 756 pg/ml at 10:00 pm), no pathologies in the imaging studies of the adrenals and the pituitary and the presence of a tumour in the superior mediastinum on a CT scan raised a suspicion of ectopic ACTH syndrome. Following preparation with aminoglutethimide, an inhibitor of adrenal steroidogenesis, the patient underwent surgical resection of the mediastinal tumour. Histopathological examination revealed thymic carcinoma with lymph node involvement. Immunohistochemistry confirmed the tumour to be a functioning one (positive NET markers: neuron-specific enolase and chromogranin A). After the surgery the patient underwent radio- and chemotherapy. The signs and symptoms of Cushing's syndrome resolved.

From 2003 onwards a gradually worsening asthenia and round facies were again observed. The imaging studies (CT) performed at the beginning of 2005 revealed a mediastinal tumour, which was subsequently resected (histopathology showed recurrent thymic carcinoma) and the patient underwent chemotherapy. The clinical manifestations of Cushing's syndrome subsided for several months. At the end of 2005, somatostatin receptor scintigraphy using OctreoScan revealed pathological tracer accumulation in the vicinity of the spine in the mediastinum on the right. A CT scan did not reveal a tumour but, in light of the persistent manifestations of Cushing's syndrome, a repeat thoracotomy was performed in March 2006 and the mediastinal adipose tissue was removed. Due to persistently elevated post-op cortisol levels, the patient was started on LAR octreotide at the dose of 20 mg IM q1m. The patient's well-being improved slightly but the hypokaliaemia and weakness persisted. In May

2006 the patient was diagnosed with diabetes mellitus and started on insulin.

In August 2006 the patient presented to the Department of Endocrinology and Diabetology, Medical College, Nicolaus Copernicus University, Bydgoszcz, Poland, with considerable weakness and severe hypokaliaemia (2.1 mmol/l). His serum cortisol levels were very high (111 μg/dl at 8:00 am [normal range: 4 38 μg/dl]). The patient was started on aminoglutethimide and his octreotide dose was increased to 30 mg q1m. During the hospitalization the patient developed clinical and biochemical manifestations of adrenal failure and the adrenal steroidogenesis inhibitor was discontinued. The patient required temporary hydrocortisone treatment. The subsequent injections of LAR octreotide at the dose of 30 mg were given in September and October 2006. During the last two months of treatment with the higher dose of octreotide the patient's well-being improved considerably. The levels of cortisol and potassium determined in October were normal (10.0 μg/dl and 4.7 mmol/l respectively), as were as his glucose levels (so that the patient no longer required insulin). The patient remains in active employment.

Case 4 — a patient with ectopic ACTH syndrome and a neuroendocrine tumour of unknown location

In November 2006 a 26-year-old male (DB) developed rapidly worsening manifestations of Cushing's syndrome (characteristic distribution of the adipose tissue, asthenia, hypertension, diabetes mellitus, and purple-blue striae). In December 2003, during hospitalization at the Department of Endocrinology and Diabetology, Medical College, Nicolaus Copernicus University, Bydgoszcz, Poland, the patient had been found to have elevated cortisol levels (40.7 μg/dl at 8:00 am, 29.4 μg/dl at 8:00 pm) and very high ACTH levels (924 pg/ml at 8:00 am and 618 pg/ml at 8:00 pm). The dexamethasone suppression test showed the pituitary aetiology of Cushing's syndrome. No pituitary microadenoma was demonstrated on MRI, but ^{99m}Tc-MIBI scintigraphy revealed pathological tracer accumulation in the pituitary gland. Following preparation with mitotane (an inhibitor of adrenal steroidogenesis) the patient underwent transsphenoidal partial resection of the pituitary gland. Histopathology did not confirm the presence of adenoma. Despite the surgery the levels of cortisol and ACTH continued to be persistently high (ACTH: 162 pg/ml at 8:00 am and 144 pg/ml at 8:00 pm). The patient was also found to have elevated serum levels of chromogranin A (22 U/l). Repeated dexamethasone suppression test indicated an adrenal or ectopic cause of the hypercortisolaemia. No abnormalities were found in the diagnostic investigations aimed at establishing the cause of the hypercortisolaemia (abdominal CT and MRI scans, chest X-ray, thyroid gland ultrasound, gastroscopy and colonoscopy). The chest CT scan showed a focus measuring 11 $\times$ 6 mm in segment 4 of the right lung. After a pulmonologist consultation a PET scan was performed, which showed no increased metabolism in the location of the lesion found on the CT scan. However, in the anterior direction from the spine, a thickening of tissues and increased glucose metabolism were observed at the level of the first cervical vertebra. The MRI scan did not visualize the focus described in the PET scan. In May 2005, total body scintigraphy with ^{131}I-MIBG revealed, in the region of the left phrenic dome and the left ventricle of the heart, an area of radiotracer accumulation, and echocardiography revealed a hypoechoic area measuring 26 $\times$ 8 mm near the lateral wall of the left ventricle. These lesions were not, however, confirmed in the MRI scan of the mediastinum. Due to the progressive asthenia, the deterioration of the patient's condition and the persistent hypercortisolaemia despite the use of ketoconazole (an inhibitor of adrenal steroidogenesis) the patient was started on octreotide 0.1 mg tid SC. An improvement in muscle strength and good blood pressure control at lower doses of anti-hypertensive medication were achieved. During the treatment the patient required initiation of a replacement dose of hydrocortisone due to the signs and symptoms of adrenal failure. Due to an unclear chest radiogram in May 2005, following preparation with octreotide, the patient underwent a thoracotomy. No neuroendocrine tumour was, however, found. Due to the persistent hypercortisolaemia, progressive emaciation and based on the diagnosis of ectopic ACTH secretion, a bilateral adrenalectomy was performed in June 2005. The surgery proved not to be radical, as the manifestations of Cushing's syndrome persisted. For this reason, the patient was started on LAR octreotide in June 2005 at the dose of 20 mg q4w. During octreotide treatment the patient developed clinical and biochemical signs of adrenal failure, which required the use of hydrocortisone at replacement doses. A considerable improvement was observed in the patient's well-being, muscle strength and the changes in body habitus (resolution of the characteristic

adipose tissue distribution, striae and round face). Glucose levels returned to normal and blood pressure decreased. In March 2006, with a view to performing somatostatin receptor scintigraphy with OctreoScan, octreotide was discontinued and the replacement dose of hydrocortisone was maintained. The cortisol levels determined at the subsequent follow-up visits fell within the low normal range. The patient has been off octreotide for the past 9 months. No clinical signs of Cushing's syndrome are observed and laboratory tests reveal normal glucose and cortisol levels. The patient still requires replacement doses of hydrocortisone despite being off octreotide.

Discussion

Native somatostatin and its analogues (octreotide, lanreotide, vapreotide) exert their biological effects by binding with somatostatin receptors. Five subtypes of the somatostatin receptor have so far been identified (SSTR-1 to -5). These receptors have been demonstrated on the surfaces of cells in pituitary tumours, carcinoid tumours and pancreatic endocrine tumours [7, 9]. Ninety percent of carcinoid tumours and 80% of pancreatic endocrine tumours express SSTR 2. Somatostatin demonstrates equal binding affinity for all of its receptor subtypes, while its analogues show high affinity for SSTR 2 and SSTR 5, moderate affinity for SSTR 3 and low or no affinity for SSTR 4 and SSTR 1 [10].

Due to its short half-life, somatostatin can exert its therapeutic effects only if given in a continuous intravenous infusion. Somatostatin analogues may be given in repeated subcutaneous injections q8h. Slow-release formulations are given intramuscularly every 4 weeks (LAR octreotide) or every 2 weeks (lanreotide PR) [9]. It is recommended to start treatment with octreotide q12h to q8h and in case of possitive effect swap to one of the long acting formulation. This allows a rapid achievement of the target serum concentration of the drug (which, in the case of slow-release formulations, is achieved within several months after administration) and relatively rapid symptom control [2, 11]. This approach was used in the four patients described in this paper during the periods of severe signs and symptoms arising from excess hormone production. Repeated subcutaneous dosing also enables the control of adverse effects, which include gastrointestinal symptoms, gall bladder dysfunction and leg cramps. Cholelithiasis may develop during long-term treatment with somatostatin analogues [2, 7, 11]. None of the patients presented in this paper developed the above manifestations during octreotide treatment. Somatostatin analogue treatment is generally well tolerated and these drugs are rarely discontinued because of adverse effects [7].

The principal effect of somatostatin analogues consists of the inhibition of active peptide and hormone release from neuroendocrine tumour cells, which leads to amelioration of symptoms related to excessive hormone secretion [7, 9, 10, 12, 13]. This effect is best documented in carcinoid syndrome. The efficacy of lanreotide at the dose of 30 mg IM q2w has been demonstrated by Ruszniewski et al. [12] in a multi-centre prospective study of 39 patients with carcinoid syndrome. At six months of treatment the incidence of flushing episodes and loose stools reduced by half in 54% and 56% of the patients respectively. In 42% of the patients the 24-hour urinary 5-HIAA excretion reduced by half [12]. A high efficacy of LAR octreotide in the symptomatic treatment of carcinoid syndrome has been demonstrated by Tomassetti et al. [13]. Diarrhoea resolved in 9 out of 10 patients and in one patient the number of bowel movements decreased from 5 to 2 a day. Flushing episodes resolved in 9 patients; in one patient the number of flushing episodes initially decreased but following an increase of the dose of the drug from 20 mg to 30 mg q4w, they resolved completely [13].

In a multi-centre European study of 55 patients with NETs, including 48 patients with carcinoid tumour, who received lanreotide at the dose of 30 mg IM q2w, a reduction in clinical symptoms was observed in 38% of the patients with carcinoid syndrome [14].

In the patient with carcinoid syndrome we describe in this paper octreotide also resulted in symptomatic improvement and a reduction in 5-HIAA excretion. Despite the fact that the disease was progressing and it was increasingly difficult to control the symptoms in the final months of the patient's life, octreotide treatment reduced the patient's suffering.

In patients with tumours secreting vasoactive intestinal peptide (VIP) and persistent symptoms (diarrhoea, hypokaliaemia), octreotide is the treatment of choice. This especially applies to patients with tumours that are inoperable or unresponsive to chemotherapy [15]. Diarrhoea improves or completely resolves in 80% of patients managed with octreotide. The clinical improvement is not always associated with reduced serum levels of VIP, which may suggest that octreotide may directly affect in-

testinal function. Octreotide treatment has also been shown potentially to modify the VIP molecule, which results in a lower biological activity of the hormone [10]. In the patient with typical clinical manifestations of a VIP secreting tumour we described above, octreotide treatment reduced the number of stools, improved the water and electrolyte balance parameters and ameliorated the patient's general condition. It should be emphasized that despite employing state-of-the-art diagnostic techniques the location of the tumour could not be established. The diagnosis was based on the characteristic clinical manifestations, exclusion of other causes, slightly elevated levels of chromogranin A (a neuroendocrine tumour marker) and the outcomes of octreotide treatment.

The efficacy of octreotide in reducing the symptoms of Cushing's syndrome in the course of ectopic ACTH secretion was first demonstrated in 1988 [16]. Treatment with octreotide reduces serum cortisol and ACTH leading to partial or complete resolution of hypercortisolaemia manifestations [17, 18]. In both patients with ectopic ACTH syndrome octreotide led to the normalization of cortisol levels and partial or complete resolution of the clinical manifestations of Cushing's syndrome.

In addition to relieving the symptoms of excessive hormone secretion by neuroendocrine tumours, somatostatin analogues exert anti-tumour effects that are mediated, among other factors, by suppressing the secretion of growth factors, such as insulin-like growth factor-1 (IGF-1) and epidermal growth factor (EGF) modulating the immune system, and by inducing apoptosis (via the SSTR-3 receptor) and inhibiting angiogenesis [10,19]. The anti-proliferative effect of somatostatin analogues is not as well-documented as their effects on the endocrine function of NETs. Most studies suggest mild to moderate effects of these drugs on tumour regression or tumour growth suppression [10]. Arnold et al. demonstrated that octreotide exerted an anti-proliferative effect in the form of tumour growth suppression in patients with metastatic gastrointestinal NETs but was given at high doses (200–300 μg SC tid) [20]. Aparicio et al. used standard doses of somatostatin analogues (octreotide 100 μg SC tid or lanreotide 30 mg IM q14d) and achieved tumour growth suppression in 57% of the patients with NETs [21].

In one of our subjects, the patient with ectopic ACTH syndrome and a tumour of unknown nature (type) and location, the potential anti-proliferative effects of octreotide could be considered. During octreotide treatment all the reversible manifestations of Cushing's syndrome subsided and have not reappeared, even though the drug has been discontinued. The patient obviously needs further monitoring.

Another aspect of treatment with somatostatin analogues is their effect on improving prognosis in patients with NETs. A Dutch epidemiological study of 2,391 patients with carcinoid tumour diagnosed between 1989 and 1997 demonstrated that the survival in patients with metastatic disease depended on the timing of diagnosis (before vs after the year 1992, when octreotide received regulatory approval). The survival time increased from 24 to 43 months with the 3-year survival rate rising from 29% to 60%. In a multivariate analysis that took into account the age, sex, location of the primary, the centre providing the treatment and the timing of the diagnosis (before vs. after the year 1992), only the last turned out to be an independent prognostic factor [22].

Although its use was interrupted, octreotide treatment prolonged survival in the patient with ectopic ACTH syndrome whom we describe in this paper, as it has been proved that the 5-year survival rate in patients with incurable hypercortisolaemia is as great as 50% [23]. In both of our patients with ectopic ACTH syndrome, octreotide treatment has been an effective and survival-prolonging form of long-term therapy that these patients could be offered by contemporary medicine.

In the patient with thymic carcinoma all the other treatment modalities, perhaps with the exception of adrenalectomy, had been attempted (surgery, radiotherapy and chemotherapy). In the patient with unknown location of the neuroendocrine tumour octreotide offers the hope that the patient will survive until the time the site of ectopic ACTH secretion can be identified. As already mentioned, regression of the tumour resulting from octreotide treatment cannot be ruled out in this case.

Treatment with somatostatin analogues, especially with slow-release formulations, improves the quality of life and patient compliance [10, 14], as was first demonstrated in the already cited multicentre study of neuroendocrine tumours. Based on the EORTC QLQ-C30 questionnaire, significant improvements in cognitive function, emotional state, perception of health and sleep disorders have been shown in patients managed with lanreotide PR [14].

Our findings in patients with NETs allow us to believe that treatment with LAR octreotide has im-

proved their quality of life. The partial or complete resolution of diarrhoea in the patient with carcinoid syndrome and the patient with manifestations of VIPoma has offered them the possibility of normal social functioning. Increased muscle strength and improved well-being have allowed the patients with ectopic ACTH syndrome to perform the activities of daily living unaided and even to resume work. The normalization of glycaemia has freed the patients from the necessity to use insulin. The resolution of the Cushingoid appearance has boosted self-esteem and self-image in the patient with unknown location of the NET.

Summary

Slow-release octreotide used in the treatment of patients with neuroendocrine tumours reduces the signs and symptoms associated with an excessive secretion of hormones and catecholamines, improves quality of life and, possibly, prolongs survival. This form of treatment is the only effective method of symptomatic relief in patients with advanced disease when surgery is either unfeasible or ineffective, and in patients with unknown location of the neuroendocrine tumour.

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