

¹¹¹In-octreotide scintigraphy: A tool to select patients with endocrine pancreatic tumors for octreotide treatment?

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The results of octreotide scintigraphy, performed in two patients with malignant endocrine pancreatic tumors, were compared with the effect of somatostatin-14 and its analogue octreotide on hormonal levels and clinical outcome. Radiolabeled octreotide failed to demonstrate any tumor localisation in a patient with a malignant insulinoma. Nevertheless, IV injection of somatostatin and octreotide resulted in a significant decrease in peripheral insulin levels. Moreover in this patient, chronic treatment with a high dose of octreotide subcutaneously was able to transiently lower the incidence of hypoglycemic events. In a second patient with metastatic PP-oma, ¹¹¹In-octreotide disclosed a pancreatic tumor in the tail of the pancreas and metastatic supraclavicular lymph nodes. In this patient IV administration of somatostatin and octreotide inhibited the hormonal secretion of the tumor but subcutaneous injection of octreotide induced hardly any decrease in plasma PP levels and failed to affect tumor growth. These observations find a possible reason for this in the heterogeneous affinity of the somatostatin receptors in endocrine pancreatic tumors. They indicate that octreotide scintigraphy alone should not be used to select patients with neuroendocrine tumors who can benefit from chronic treatment with the somatostatin analogue.

Key words: octreotide, endocrine pancreatic tumors, scintigraphy

INTRODUCTION

SCINTIGRAPHIC IMAGING with ¹¹¹In-octreotide, a somatostatin analogue, has been proposed in the management of patients suspected of having somatostatin receptor positive tumors. Somatostatin receptors have been demonstrated on a variety of human tumors, including those with amine precursor uptake and decarboxylation (APUD) characteristics.^{1,2} Among these APUD tumors, particularly endocrine pancreatic tumors can present with a variety of clinical symptoms predominantly related to the their main hormonal hypersecretion. Somatostatin and its analogues have been shown to inhibit hormonal secretion of most of the pancreatic endocrine tumors, thereby overcoming life-threatening biological disturbances such as hypoglycemia in insulinoma or severe hypokalemia and fluid losses in the WDHA syndrome.^{3,4} They have also been reported to suppress tumor growth in some patients.⁵

In the light of these observations, the use of ¹¹¹In-octreotide has been proposed not only for imaging of endocrine pancreatic tumors and their extension, but also for the determination and prediction of a potential beneficial effect of somatostatin on tumoral secretion and growth.⁶⁻⁸ ¹¹¹In-octreotide scintigraphy, applied to differentiate those patients who have somatostatin receptor positive tumors from those who do not, could therefore indicate the need for further daily treatment of the patient with somatostatin or its analogue.

In this report these statements are challenged. The effect of intravenously administrated somatostatin and octreotide on hormonal secretion is compared with the clinical outcome during daily s.c. octreotide treatment in two patients bearing a generalized malignant endocrine pancreatic tumor, one with positive scintigraphy with ¹¹¹In-octreotide and one with negative imaging.

MATERIALS AND METHODS

¹¹¹In-octreotide scintigraphy

Two patients with malignant endocrine pancreatic tumors received 110 MBq ¹¹¹In-pentetreotide (OctreoscanR111,

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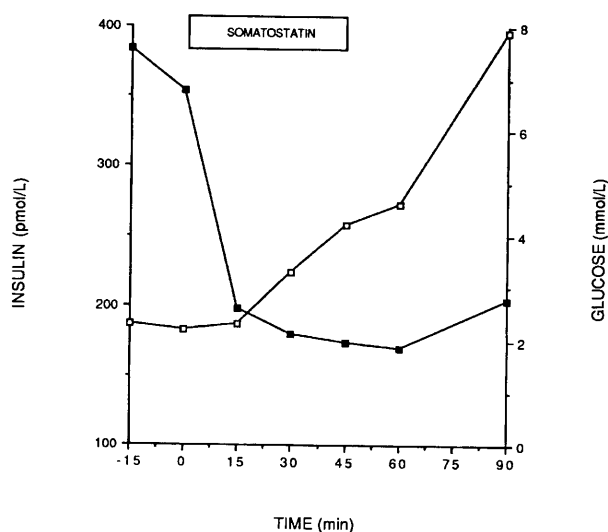


Fig. 1 Plasma glucose (open squares) and insulin levels (closed squares) following IV. somatostatin (patient 1).

Malinckrodt Medical) in one single intravenous injection, once at diagnosis and once when extension of liver metastases was demonstrated on a CT scan during evolution. Scintigraphic imaging was performed 24 hours after administration and was repeated at 48 hours. Planar whole body images were obtained with a large field of view camera equipped with a high energy all purpose collimator on a Siemens Bodyscan R system.

Hormone assays

Insuline, glucagon, gastrin, GRP and calcitonin were determined with commercially available kits. Pancreatic Polypeptide (PP) was measured by radioimmunoassay following the method by Adrian.⁹ The PP antibody, porcine PP for labelling and human PP (standard) were a gift from Dr. R.E. Chance (Eli Lilly, Indianapolis, USA). The normal reference interval accepted is 0–115 pmol/L.

Somatostatin and octreotide administration

Intravenous somatostatin (Somatostatin, UCB) was given in a bolus injection of 250 µg, followed by a continuous infusion of 500 µg/h for 45 min. Blood samples were drawn for determination of peripheral hormone levels and glucose at –15, 0, 15, 30, 45, 60 and 75 min. A similar test was then conducted with octreotide (Sandostatin R, Sandoz) in a bolus dose of 100 µg and continuous IV infusion of 200 µg/h. Prolonged daily treatment with octreotide was administered subcutaneously either in a bolus up to 200 µg tid or in a continuous infusion up to 2000 µg/day.

RESULTS

Patient 1

A 35-year-old man was hospitalized after he had fainted

during triathlon training. Blood glucose was 28 mg/dl on admission. An increased insulin/glucose ratio in the presence of hypoglycemia pointed to a diagnosis of insulinoma. An abdominal CT scan failed to show any pancreatic tumor or metastatic lesions in the liver. With selective arteriography of the pancreatic vessels, a tumor with a diameter of 2–3 cm was detected in the tail of the pancreas. The appearance of multiple small blushes in the liver during the venous phase was suggestive of liver metastases. None of these lesions could be evidenced by ¹¹¹In-octreotide scintigraphy. During surgery, a tumor at the tail of the pancreas was removed by distal pancreatectomy and the presence of liver metastases was noted. Histopathological examination confirmed the diagnosis of malignant insulinoma. Clinical evolution was characterized by failure to respond to various chemotherapies (Streptozotocin/5-Fluorouracil; Carboplatinum/Etoposid; Streptozotocin/Doxorubicin given consecutively over a 2 year period) with frequent life threatening episodes of hypoglycemia in spite of the administration of diazoxide at a dose of up to 600 mg/day. Multiple liver metastases 2 cm in diameter could be detected by CT scan. Prior to s.c. treatment with octreotide, again no imaging of any tumor site could be evidenced by a second ¹¹¹In-octreotide scan. Intravenous injection of somatostatin inhibited insulin levels more than 50 percent (Fig. 1) and induced an increase of plasma glucose levels. A similar result was noted during octreotide infusion. Prolonged s.c. treatment with high dose octreotide (2000 µg/day) was therefore initiated. This resulted in a reduction of peripheral insulin levels from 385 ± 90 to 242 ± 25 pmol/L (mean of 3 measurements ± SD), in higher 24 hour blood glucose profiles and a 6 month period without major hypoglycemic insults. Concomitantly the dose of diazoxide was able to be lowered to 200 mg.

Patient 2

A 49-yr-old woman presented with a left supraclavicular mass. No other clinical signs were seen. Biopsy of a supraclavicular lymph node demonstrated the existence of a metastatic endocrine tumor. Immunocytochemistry showed the presence of pancreatic polypeptide (PP) positive cells, thereby indicating the pancreatic origin of the metastatic cells. Peripheral plasma levels of insulin, glucagon, gastrin, GRP, calcitonin and PP were within normal limits. Computed tomography of the abdomen revealed multiple liver metastases together with tumoral lesions in the tail of the pancreas. A diagnosis of a non-functioning endocrine pancreatic tumor was put forward.

An ¹¹¹In-octreotide scan was done. This isotopic imaging technique pointed to the presence of somatostatin receptor positive cells at the level of the supraclavicular mass and in the tail of the pancreas but not in the liver (Fig. 2). Chemotherapy (Streptozotocin/5-Fluorouracyl every 4 weeks for the first 3 months and then Streptozotocin/Doxorubicin¹⁰ for 6 months) failed to effect any regres-

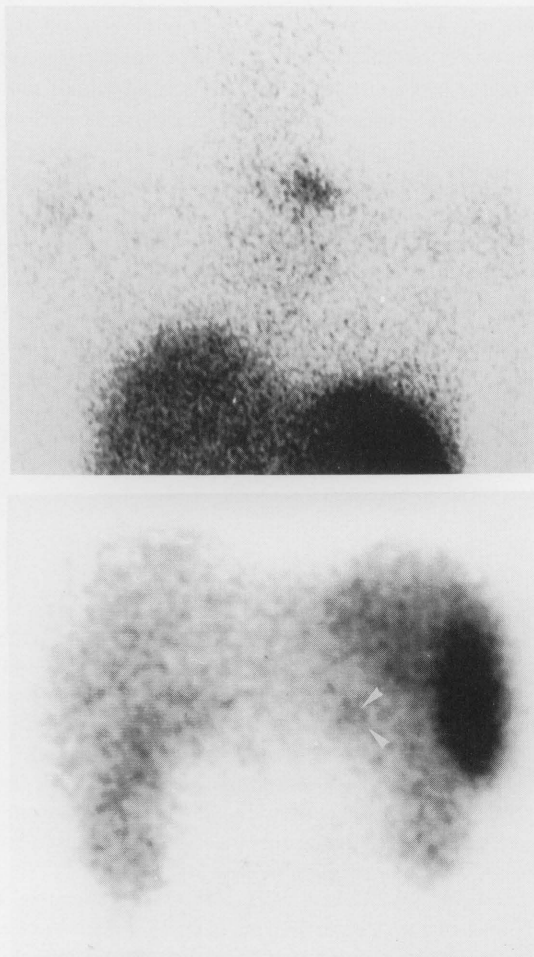


Fig. 2 ^{111}In -octreotide imaging of the left supraclavicular mass (upper panel) and pancreas (lower panel; white arrows) (patient 2).

sion of the disease. On the contrary, an increase of the number of liver metastasis was detected by means of a CT scan. Peripheral plasma PP levels progressively rose to pathological levels (up to 1500 pmol/L) as did glucagon levels (up to 153 pmol/L). A second octreotide scintigraphy, performed when extension of liver metastases was apparent on CT scan, appeared to be comparable to the first one.

Intravenous administration of somatostatin (Fig. 3, upper panel) or octreotide (Fig. 3, lower panel) at different times of clinical evolution resulted in a marked inhibition of PP. Glucagon levels were also decreased with about 40% by both agents. However, subcutaneous injection of octreotide in a bolus (100 μg t.i.d. during 3 weeks) did not induce any decrease in peripheral PP levels, while administration of 200 mg t.i.d. only resulted in an insignificant decrease in the peripheral hormone levels from 1040 to 980 pmol/L. Even continuous infusion of octreotide (1000 μg daily for three weeks) only resulted in a slight decrease in circulating PP (from 980 to 894 pmol/L). Glucagon levels rose from 106 pmol/L to 153 pmol/L for the entire

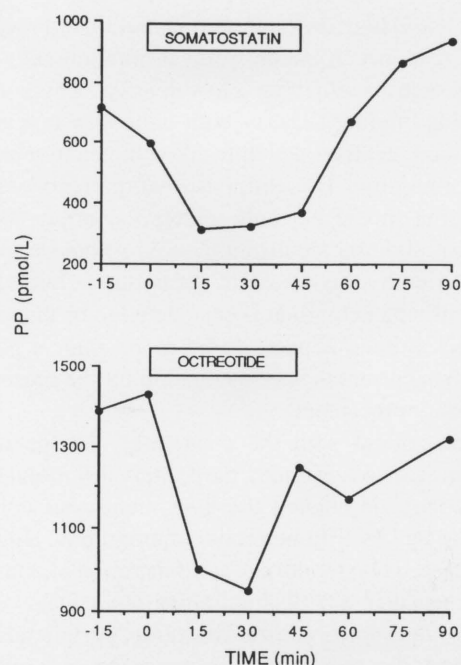


Fig. 3 Effect of IV somatostatin (upper panel) and octreotide (lower panel) on peripheral plasma PP levels (patient 2).

treatment period. During s.c. octreotide treatment (approximately seven weeks) a further increase in the number and size of liver metastases was demonstrated on a CT scan.

DISCUSSION

These case reports of two endocrine pancreatic tumors show evident discrepancies between the results of scintigraphy with radiolabeled octreotide and the effect of either acute or chronic administration of the somatostatin analogue on hormonal secretion and the clinical outcome. Such findings are in contrast with earlier reports which claimed that ^{111}In -octreotide imaging may predict the responsiveness to therapy with this compound.⁶⁻⁸

In the case of the malignant insulinoma here described, ^{111}In -octreotide failed to show any *in vivo* receptor binding at the level of the primary tumor or on the level of liver metastases. Lamberts et al.⁸ were also unable to visualize the tumoral lesions with ^{111}In -octreotide scintigraphy in 3 out of eight patients with a proven insulinoma in contrast to 10 gastrinomas, one glucagonoma and 2 nonfunctioning endocrine tumors that were all clearly localized. According to these authors a negative scan could be explained by the absence of octreotide receptors on some of these tumors. Their hypothesis was substantiated by the detection *in vitro* of somatostatin receptors in only 72% of the insulinomas. In these cases a low dose of octreotide s.c. (50 μg) did not suppress hormonal hypersecretion. In our patient, however, intravenous somatostatin-14 and octreotide were able to transiently reduce peripheral insu-

lin levels and high dose s.c. administration did result in a clinical response. Apparently, the insulinoma cells in this case presented with either a low density of high affinity octreotide binding sites, or with only very low affinity octreotide receptors, which resulted in negative scintigraphic imaging. This implies that patients with an insulinoma should not only undergo scintigraphy with ^{111}In -octreotide for localization purposes but should also be tested with a high dose of octreotide before chronic treatment with octreotide is considered to be inappropriate. This attitude appears to be more clinical practice rather than current *in vitro* evaluation for the presence of somatostatin receptors.

In the patient with the apparently non-functioning endocrine pancreatic tumor, the primary lesion and lymph node metastasis but not the liver metastases could be demonstrated by ^{111}In -octreotide scintigraphy. However, in this case, a two month s.c. administration of octreotide did not result in any decline in the tumor mass. On the contrary, during the clinical evolution, peripheral levels of PP and glucagon gradually increased and, although inhibited by intravenous administration of somatostatin-14 and its analogue, could not be lowered by s.c. octreotide on a daily basis. As in the patient with an insulinoma, no scintigraphic imaging of the multiple liver metastases was obtained even 48 hours post injection of ^{111}In -octreotide. In the case of the PP-oma, however, octreotide receptors could be demonstrated on the tumor in other sites by ^{111}In -octreotide scan and be evidenced by reduced hormonal secretion after intravenous injection of octreotide. This could point to the existence of metastatic cells in the liver lacking high affinity somatostatin receptors. More likely it underlines difficulties with ^{111}In -octreotide imaging in detecting small liver lesions.

Evidence of a positive effect of octreotide on tumor growth of endocrine pancreatic tumors is scarce. In a review, Gorden et al. reported that out of a total of 46 patients with metastatic endocrine pancreatic tumors who had been treated for several weeks with octreotide, a decrease in tumor size was only observed in eight patients.⁵ The further increase in the tumor mass in our patient during octreotide treatment could well account for the apparent contradictory finding of a positive ^{111}In -octreotide scan and reduced hormonal hypersecretion

following IV octreotide administration and its minor effect on peripheral PP levels during prolonged treatment. Indeed the possibility that the daily s.c. administration of octreotide did overcome a further increase in peripheral PP levels due to tumoral growth cannot be excluded.

In conclusion, some studies have attributed a major place for octreotide scintigraphy in the management of endocrine pancreatic tumors.⁶⁻⁸ The clinical evolution of two patients with endocrine pancreatic tumors, described in this report, suggests that scintigraphy with the actual somatostatin analogues should be used carefully for the prediction of a potential therapeutic effect.

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