*Journal of BUON* **14:** 135-138, 2009


*SHORT COMMUNICATIONS AND CASE REPORTS*

# Hypoglycemia induced by long-acting somatostatin analogues in a patient with nonfunctional neuroendocrine tumor

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## Summary

*Somatostatin and its long-acting analogues are effective in symptom control in patients with functional neuroendocrine tumors; they are also able to control tumor growth. Somatostatin analogues are safe and generally well tolerated. In some cases they may cause serious complications.*

*Somatostatin analogues are potent inhibitors of growth hormone (GH) and glucagon secretion. They cause impairment of hepatic glucose output and delay in intestinal absorption of carbohydrates. Patients with huge tumor mass and multiple liver metastases have increased risk of tumor-induced hypoglycemia. In these patients, long-acting octreotide may trigger serious hypoglycemia. The patients whose glucose control is dependent on counter-regulatory hormones should be monitored for the possibility of hypoglycemia. Herein, we present a patient with severe and prolonged hypoglycemia after long-acting octreotide treatment.*

**Key words:** hypoglycemia, neuroendocrine tumor, somatostatin analogues

## Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) constitute a group of tumors that generally grow slowly. Surgery is the best treatment, but some metastatic or rapidly growing neuroendocrine tumors require systemic treatment. Since most neuroendocrine tumors express high levels of somatostatin receptors, somatostatin analogues are used frequently to control hormonal symptoms, more rarely to slow down the growth of tumor [1,2].

Somatostatin analogues (octreotide, lanreotide, and long-lasting release [LAR] octreotide) mediate their effects on hormone secretion by the tumor cell octreotide and their antiproliferative effects predominantly through somatostatin receptor (SSTR) 2 [2]. Somatostatin inhibits the release of several intestinal peptides and modulates growth factors like insulin-like growth factor-I and -II (IGF-I, IGF-II) [3]. Stabilization of tumor growth occurs in 30-50% of patients with GEP NETs [2,4] while objective tumor responses occur in 5-15% of those patients [5,6]. So far, somatostatin analogues have been used as possible antineoplastic agents in the treatment of functional and nonfunctional NETs [2,4].

Somatostatin analogues are safe, easy to use and generally well tolerated. Treatment discontinuation due to adverse effects is rare [5,6]. Side effects of somatostatin analogues are flatulence, diarrhea, abdominal pain, steatorrhea, nausea, vomiting, hyperglycemia or hypoglycemia, leg cramps, blurred vision, night sweats, and pain at the injection site [5]. There are few reports in the literature about hypoglycemia following somatostatin analogues in patients with Type 1 and Type 2 diabetes mellitus [7], acromegaly [8,9], proinsulinoma [10], and carcinoid tumor [11] and malignant mesenchymal tumors [12].

Herein, we report a case with severe and prolonged hypoglycemia triggered by a long-acting analogue of somatostatin in a patient with non-functional pancreatic neuroendocrine tumor.

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Received 02-01-2008; Accepted 09-02-2008

## Case presentation

A 53-year-old lady was admitted to our hospital because of abdominal pain and distention. On her physical examination, hepatosplenomegaly was detected. Computerized tomography (CT) of the thorax and abdomen showed a large mass in the pancreas and multiple metastatic lesions in the lung, liver and spleen (Figure 1). Tumor invasion was detected in the spleen. These radiological findings indicated an unresectable pancreatic cancer. A biopsy from the pancreatic lesion was performed and the pathological examination revealed a well differentiated neuroendocrine carcinoma (Figure 2A and 2B). Octreotide scintigraphy showed an intense uptake corresponding to the pancreatic lesion (Figure 3).

Her complete blood count, blood biochemistry, and thyroid function tests values were normal. The results of the serum hormonal analysis were as follows: insulin 9.47 μU/mL (normal 5-20), calcitonin 10 ng/L (normal <30), gastrin 46 ng/L (normal <60) and parathyroid hormone 25.7 pg/mL (normal 10-65). The urine 5-hydroxyindoleacetic acid excretion was normal (2.52 mg/d; normal 2-10). A diagnosis of nonfunctional pancreatic NET had been made by the clinical and endocrinological findings.

Treatment with interferon (IFNα-2b), 5 million IU subcutaneously (sc), 3 times a week and the somatostatin analogue octreotide (sandostatin®) 0.1 mg sc, 3 times a day, started. One month after this therapy, LAR octreotide formulation (sandostatin LAR®, 20 mg), once a month, was administered instead of the short-acting analogue. Ten days after the second LAR octreotide injection, she was admitted to our hospital with loss of consciousness. On her admission, plasma glucose level was 14 mg/dl (normal 70-110). Fifty ml of a 30% dextrose solution were given immediately as an i.v. bolus, and subsequently 17.5% dextrose infusion started. The patient's mental status improved gradually within 30 min and the blood glucose level increased to 75 mg/dl after the parenteral dextrose infusion. She had no history of diabetes and was not on any medication such as oral antidiabetic or insulin which could cause hypoglycemia.

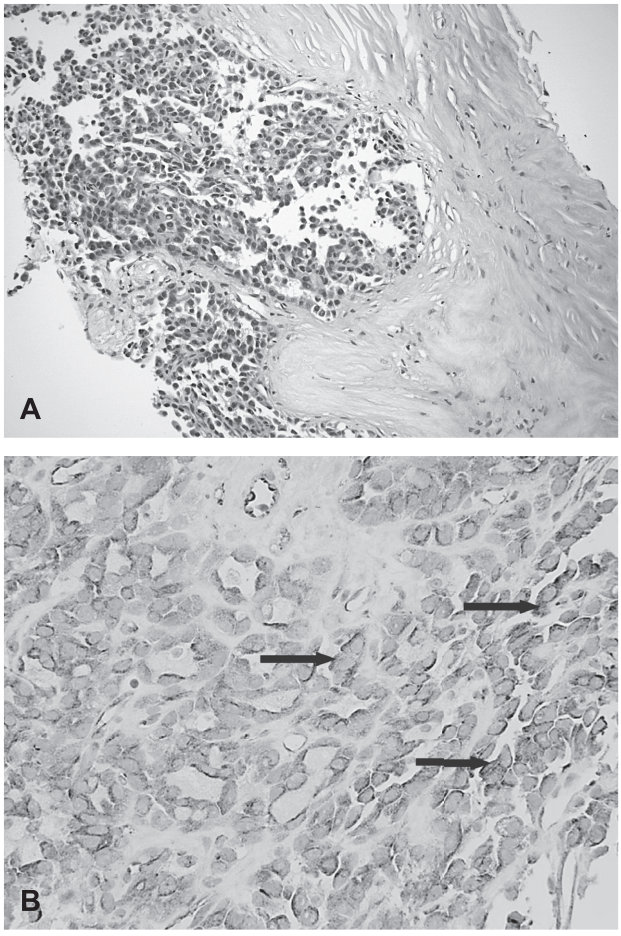


**Figure 2. A:** Uniform tumor cells in a fibrotic stroma (H&E ×10), **B:** Immunohistochemical staining shows diffuse chromogranin A positivity in the cytoplasm of tumor cells (arrows; ×200).

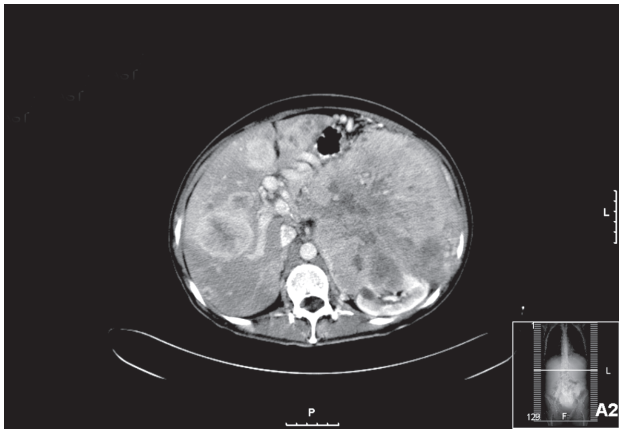


**Figure 1.** Computerized tomography of the abdomen shows a large mass in the pancreas and multiple metastatic lesions in the liver.

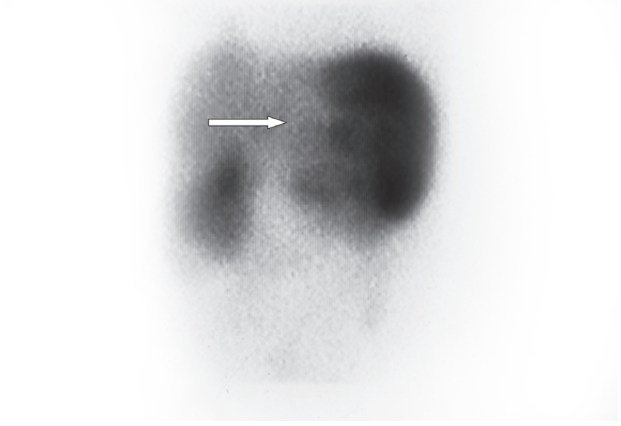

**Figure 3.** Octreotide scintigraphy shows an intense uptake corresponding to the pancreatic lesion (arrow).

At the time of hypoglycemia, insulin (< 2.0 μIU/ml; normal 6.0-28.4) and c-peptide (0.533 ng/ml; normal 1.1-5.0) were suppressed, plasma cortisol was high (41.6 μg/dl; normal 5-25), insulin-like growth factor binding protein-III (IGFBP-III) was 3.54 μg/ml (normal 3.4-6.8), and IGF-I was below normal (<25 ng/ml; normal 69-358). Her liver function tests values were minimally elevated: aspartate aminotransferase 76 U/L (normal 5-34), alanine aminotransferase 27 U/L (normal 0-55), γ-glutamyl transpeptidase 58 U/L (normal 9-36), alkaline phosphatase 606 U/L (normal 40-150), total bilirubin 0.16 mg/dl (normal 0.2-1.2), serum albumin 2.6 g/dl (normal 3.5-5), prothrombin time 14.65 sec (normal 11.23-14.44). A CT scan of the abdomen revealed minimal progression of liver metastases. It was seen that the liver metastases did not result in sufficient destruction of hepatic tissue to cause impaired glucose production and hypoglycemia.

Despite sufficient oral nutrition, hypoglycemia recurred following cessation of parenteral dextrose infusion. So, we continued infusion for 6 weeks to maintain normoglycemia. A carbohydrate-rich diet at frequent intervals was given. Methylprednisolone was added to increase neoglucogenesis. The dextrose infusion rate was tapered and stopped. Stability of blood glucose level was achieved with methylprednisolone 48 mg/day and a high caloric diet at frequent intervals. The patient was discharged from the hospital, and home blood glucose monitoring revealed normoglycemia and no further attacks have occurred. The methylprednisolone dose was decreased gradually and 8 weeks after discharge it was stopped. Chemotherapy containing cisplatin and etoposide was planned but it couldn't be administered because of pneumonia. She was out of follow-up for 25 days. Four months after the first hypoglycemic attack, she presented to the emergency room with loss of consciousness. At presentation, her serum glucose level was 12 mg/dl. A CT scan of the thorax and abdomen revealed significant progression of liver and lung metastases. Because of progressive metastatic disease and poor oral intake, i.v. dextrose infusion was started and maintained until her death.

## Discussion

Hypoglycemia secondary to somatostatin analogues is rarely reported in the literature [7-12]. Causes for somatostatin analogue-induced hypoglycemia can be explained by different mechanisms. Somatostatin inhibits intestinal motility so transit time is increased. Several studies have shown that somatostatin inhibits nutrient absorption and exerts inhibitory effects on splanchnic hemodynamics [13,14]. Both the native somatostatin and octreotide inhibit glucagon secretion. Glucagon influences blood glucose mainly by regulation of hepatic glucose production. The octreotide-associated changes in blood glucose levels can be explained by rapid changes in hepatic glucose production [15]. Octreotide, an analogue with a longer half-life, has greater pharmacological activity than the native molecule (being at least 20 times more potent in suppressing GH secretion *in vivo*), and is more selective for the inhibition of GH than insulin [14]. Octreotide also inhibits normal GH secretion in response to exercise, insulin-induced hypoglycemia [14,16,17]. Both native somatostatin and octreotide have been shown to be able to suppress the glucagon and GH, but not the cortisol or catecholamine response to insulin-induced hypoglycemia [15,16]. Causes for hypoglycemia following somatostatin analogues may be suppression of these counter-regulatory mechanisms and/or delay in nutrient absorption. Enhancement of peripheral glucose utilisation by somatostatin should also be considered as a cause of hypoglycemia [15,18].

In oncology the most common cause of chronic hypoglycemia is an insulin-secreting islet-cell tumor; the next most common cause is a tumor producing IGF-II.

The triad of hypoglycemia, a non-islet-cell tumor, and hypoinsulinemia, in addition to low IGF-I and IGFBP-III levels, and normal or modestly elevated IGF-II levels are indicative of non-islet-cell tumor hypoglycemia (NICTH) [19]. The levels of serum total IGF-II (including normal and Big IGF-II) are often within normal range, and the reason is that the tumor produces an increased amount of IGF-II, which is poorly processed. Therefore, a high-molecular-weight form of IGF-II (Big IGF-II) that cannot be detected by routine IGF-II assays is released into circulation. It appears more likely that changes in the bioavailability rather than in the absolute levels of IGF-II are of importance in the induction of hypoglycemia [20]. In the present case, insulin and c-peptide levels were suppressed and plasma cortisol level was high at the time of hypoglycemia. The levels of GH, glucagon, and Big IGF-II could not be measured because of unavailability. The levels of IGF-I and IGFBP-III were low.

Liver failure in patients with liver metastases and increased glucose consumption by the tumor are less common causes of tumor-induced hypoglycemia, as spared hepatic tissue is often able to compensate with enough glucose output to maintain euglycemia. In these patients, additional factors contribute to the development of hypoglycemia [19]. In our patient, there were a huge tumor mass and multiple liver metastases. Before

the octreotide treatment, she did not experience severe hypoglycemia since her counter-regulatory hormones were intact. With the injection of octreotide, severe hypoglycemia was triggered.

The only effective treatment of NICTH is surgical removal of the tumor. However, in inoperable cases, high doses of glucocorticoid (30-60 mg/d) effectively inhibit recurrent hypoglycemia since glucocorticoids have been shown to stimulate neoglucogenesis [21]. In the present case, surgical resection was impossible and hypoglycemia occurred repeatedly despite the continuous infusion of dextrose. Therefore, methylprednisolone (Prednol®, 48 mg/day) was started and resulted in adequate control of her hypoglycemia. In this patient, hypoglycemia was prolonged. The dextrose infusion requirement lasted 6 weeks. The patient also received glucocorticoid therapy for 2 months to maintain normoglycemia. It was reported that a single dose of sandostatin® LAR provided a plateau serum level of octreotide for approximately 54 days after injection [2]. Additionally, Priou et al. reported that following sandostatin® LAR injection, suppression of counter-regulatory hormones lasted 2 months [22].

In summary, in our patient it is possible that overproduction of Big IGF-II by the tumor in combination with octreotide might play a role in the onset of hypoglycemia in the presence of decreased hepatic glucose output associated with tumor destruction of the liver and increased glucose consumption by the tumor. If octreotide is used in the treatment of patients with great tumor mass and multiple liver metastases, the possibility of hypoglycemia should be kept in mind. The long-acting somatostatin analogues may trigger serious and prolonged hypoglycemia in patients whose glucose control is dependent on counter-regulatory hormones. Glucocorticoid therapy may be effective therapeutic method in the control of hypoglycemic attacks.

## References


1. Barakat MT, Meran K, Bloom SR. Neuroendocrine tumours. Endocr Rel Cancer 2004; 11: 1-18.
2. Arnold R, Simon B, Wied M. Treatment of neuroendocrine GEP tumours with somatostatin analogues. Digestion 2000; 62 (Suppl 1): S84-S91.
3. Öberg K. Neuroendocrine gastrointestinal tumors- a condensed overview of diagnosis and treatment. Ann Oncol 1999; 10 (Suppl 2): S3-S8.
4. Plöckinger U, Rindi G, Arnold R et al. Guidelines for the Diagnosis and Treatment of Neuroendocrine Gastrointestinal Tumours. Neuroendocrinology 2004; 80: 394-424.
5. Delaunoit T, Rubin J, Neczyporenko F, Erlichman C, Hobday TJ. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors. Mayo Clin Proc 2005; 80: 502-506.
6. Polyzos A, Tsavaris N, Vafiadis I et al. Phase II study of gemcitabine plus 5-fluorouracil biologically modulated by folinic acid plus long-acting formulation of octreotide (LAR) in patients with advanced pancreatic cancer. J BUON 2005; 10: 357-364.
7. Lunetta M, De Mauro M, Le Moli R, Nicoletti F. Effects of octreotide on glycaemic control, glucose disposal, hepatic glucose production and counterregulatory hormones secretion in type 1 and type 2 insulin treated diabetic patients. Diabetes Res Clin Pract 1997; 38: 81-89.
8. Webb SM, Ortega E, Rodriguez-Espinosa J, Mato ME, Corcoy R. Decreased insulin requirements after LAR-octreotide but not after lanreotide in an acromegalic patient. Pituitary 2001; 4: 275-278.
9. Popovic V, Nesovic M, Micic D et al. Hypoglycemia in acromegalic patients treated with long acting somatostatin analogue (SMS 201-995). Horm Metab Res 1989; 21: 282-284.
10. Gama R, Marks V, Wright J, Teale JD. Octreotide exacerbated fasting hypoglycaemia in a patient with a proinsulinoma; the glucostatic importance of pancreatic glucagon. Clin Endocrinol (Oxf) 1995; 43: 117-120.
11. Brunner JE, Kruger DF, Basha MA, Meiri E, Kaatz SS. Hypoglycemia after administration of somatostatin analog (SMS 201-995) in metastatic carcinoid. Henry Ford Hosp Med J 1989; 37: 60-62.
12. Sari R, Altunbas H, Ozdogan M, Gurer EI, Karayalcin U. Severe and prolonged hypoglycemia triggered by long-acting octreotide in a patient with malignant mesenchymal tumor: Case report. J Chemother 2003; 15: 85-88.
13. Gyr KE, Meier R. Pharmacodynamic effects of sandostatin in the gastrointestinal tract. Digestion 1993; 54 (Suppl 1): S14-S19.
14. Harris AG. Somatostatin and somatostatin analogues: pharmacokinetic and pharmacodynamic effects. Gut 1994; 35 (3 Suppl): S1-S4.
15. Stehouwer CDA, Lems WF, Fischer HRA, Hackeng WHL, Naafs MAB. Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatin®). Acta Endocrinol (Copenh) 1989; 121: 34-40.
16. Christensen NJ, Christensen SE, Hansen AP, Lundboek K. The effect of somatostatin on plasma noradrenaline and plasma adrenaline concentrations during exercise and hypoglycemia. Metabolism 1975; 24: 1267-1272.
17. Adamson U, Efendic S, Lins PE, Wajngot A. Effect of somatostatin on insulin-induced hypoglycemia in man. Acta Med Scand 1982; 212: 33-37.
18. Wu MS, Ho LT, Chen YD, Reaven GM. Somatostatin potentiation of insulin-induced glucose uptake in normal individuals. Am J Physiol 1986; 251: E674-679.
19. Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. Cancer 1998; 82: 1585-1592.
20. Frystyk J, Skjaerbaek C, Zapf J, Orskov H. Increased levels of circulating free insulin-like growth factors in patients with non-islet cell tumour hypoglycemia. Diabetologia 1998; 41: 589-594.
21. Bourcigaux N, Arnault-Ouary G, Christol R, Perin L, Charbonnel B, Le Bouc Y. Treatment of hypoglycemia using combined glucocorticoid and recombinant human growth hormone in a patient with a metastatic non-islet cell tumor hypoglycemia. Clin Ther 2005; 27: 246-251.
22. Priou A, Levesque G, Simonetta C, Lancranjan I, Roger P, Jaquet P. Long acting sandostatin (sandostatin LAR) in the treatment of acromegaly. Ann Endocrinol (Paris) 1995; 56: 213-218.