Aggravation of hypoglycemia in insulinoma patients by the long-acting somatostatin analogue octreotide (Sandostatin®)


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Abstract. Recently somatostatin analogues were successfully used to control insulin-induced hypoglycemia in patients with insulinoma. We observed a transient decrease in glucose levels and symptomatic hypoglycemia after administration of the long-acting somatostatin analogue octreotide (Sandostatin®) in two insulinoma patients. We studied the acute effects of octreotide (administered before breakfast) on blood glucose and glucoregulatory hormones in these patients. In one patient, we studied the effects of glucagon replacement and changing the time of breakfast (relative to octreotide administration) on octreotide-associated changes in blood glucose and glucoregulatory hormones. Compared with control levels, octreotide therapy reduced insulin levels. During hypoglycemia glucagon and growth hormone levels were suppressed, but cortisol levels appropriately increased. The increase in catecholamine levels was normal in one patient, but markedly attenuated in the other. A transient decrease in serum glucose after octreotide was absent after glucagon replacement, but present when breakfast was taken before administration of octreotide. We conclude that in patients with insulinoma, octreotide therapy may be associated with clinically important hypoglycemia, during which counterregulatory hormone secretion may be attenuated.

Patients with insulin-secreting islet cell tumours are at risk for severe hypoglycemia. Surgical removal of the tumour is the treatment of choice. Medical therapy is often required in the period preceding surgery and in patients with metastatic disease. Recently, long-acting somatostatin analogues were successfully used to control insulin-induced hypoglycemia in patients with insulinoma (1–5).

Important advantages of long-acting somatostatin analogues compared with native somatostatin are their prolonged half life, the possibility of subcutaneous administration, and the lack of a rebound increase in insulin levels after discontinuing treatment. Furthermore, no clinically important adverse effects during short-term therapy have been reported in insulinoma patients (1–5). We recently observed a transient aggravation of hypoglycemia associated with treatment with the long-acting somatostatin analogue octreotide (SMS 201-995, Sandostatin®) in a patient with malignant insulinoma (6). We here report the acute effects of octreotide on blood glucose and glucoregulatory hormones in this patient and in a second one in whom we observed a similar worsening of hypoglycemia after administration of octreotide.

Patients and Methods

Patient A, a 77-year-old woman, was admitted with a hypoglycemic coma (blood sugar 2.0 mmol/l) at 05.00 h. After iv administration of glucose she regained consciousness. There was no history of liver disease, alcohol abuse, use of hypoglycemic drugs or prolonged (> 10 h) fasting. Results of diagnostic fasting, abdominal ultrasound and computed tomography were compatible with a diagnosis of fasting hypoglycemia due to a pancreatic insulinoma.
Patient B, a 50-year-old man, was admitted with dysarthria and confusion. His blood sugar was 0.9 mmol/l. After iv administration of glucose his symptoms disappeared. His history revealed ‘fainting spells’ which had started 6 weeks earlier, but was otherwise unremarkable. Results of diagnostic fasting, abdominal ultrasound and selective arteriography were compatible with a diagnosis of fasting hypoglycemia due to a pancreatic insulinoma.

Both patients gave informed consent to study the effects of therapy with octreotide. After these studies, both patients were operated upon. In patient A a 3 × 2 × 2 cm tumour was found in the tail of the pancreas and subsequently removed, but metastases were present both in the omentum and in the liver. In patient B a tumour with a diameter of 1 cm was found in the head of the pancreas and removed. Histological and immunological examination confirmed the diagnosis in both patients.

Study protocol
Glucose, C-peptide, insulin, glucagon, noradrenaline, cortisol and growth hormone levels were obtained on a control day and after administration of octreotide (50 μg sc). The diet was identical on both days. Breakfast consisted of tea (without sugar) and two slices of bread with butter and cheese. The patients received 750 ml 5% dextrose iv from 21.00 to 07.00 h in order to minimize the chance of nocturnal hypoglycemia. Times of meals, drug administration and blood sampling are indicated in Fig. 1. Blood samples were always taken just before meals and octreotide administration when these coincided with sampling times.

As stated above we observed a transient decrease of blood glucose levels in both patients after administration of octreotide before breakfast. To investigate possible causes of this phenomenon we further studied the effects of changing the time of breakfast (relative to octreotide administration) as well as the effects of glucagon substitution on octreotide-associated changes in blood glucose and glucoregulatory hormones in patient B. The composition of breakfast was identical on all study days. Glucagon (Novo A/S, Denmark) was dissolved in 0.9% sodium chloride containing 1% human serum albumin and infused at a rate of 0.6 ng per kilogram per min. Other details of the protocol are given in Fig. 2. During all studies a physician was present and assessed adrenergic and neuroglycopenic symptoms.

Laboratory methods
Serum glucose levels were measured with a glucose oxidase method. Adrenalin and noradrenalin were measured by a radio-enzymatic assay (7); serum C-peptide (normal fasting: 0.18–0.63 nmol/l) and glucagon (Novo Biolabs, Bagsvaerd, Denmark), insulin (normal fasting: <20 mU/l), growth hormone (WHO Standards 66/304 and 66/217, respectively), and cortisol (Autopak, ICN Biomedicals, High Wycombe, USA) were measured with radiodimmunochemical methods.

Results
In both patients mild hypoglycemic signs were observed between 08.00 and 08.15 h on the control day. In both patients these signs consisted of tremor, sweating and slight difficulty in performing simple arithmetic. During hypoglycemia, insulin and C-peptide levels did not decrease. Counter-regulatory hormone levels (except for growth hormone in patient B) increased (Fig. 1, closed circles). After administration of octreotide, severe hypoglycemic signs were observed between 08.00 and 08.30 h. Shortly after breakfast patient A lost consciousness for approximately 2 min and remained confused for approximately 10 min. Patient B became confused and dysarthric, again shortly after breakfast. For approximately 10 min he was unable to recall recent events or perform simple tasks. Insulin and C-peptide levels were lower than on the control day. Glucagon and GH responses to hypoglycemia were absent. Cortisol levels increased. Catecholamine levels rose in patient B, but not in patient A (Fig. 1, open circles).

As stated above, additional studies were performed in patient B (Fig. 2). When breakfast was taken before administration of octreotide, no hypoglycemic signs were observed. A slight transient decrease in glucose levels was nonetheless present between 08.15 and 08.45 h. Insulin and C-peptide levels increased. Glucagon levels decreased. GH, cortisol and catecholamine levels did not increase. When glucagon was replaced, no decrease in glucose levels after octreotide was observed. Furthermore, no hypoglycemic symptoms were present. Insulin and C-peptide levels increased slightly. GH, cortisol and catecholamine levels did not increase.

After surgery patient A was treated with streptozocin and, after 2 years, remains in complete remission. In patient B glucose and insulin levels returned to normal postoperatively. No further attacks have occurred.

Discussion
In these patients with insulin-secreting tumours octreotide reduced insulin levels. Nevertheless, glucose levels transiently decreased and in both patients clinically significant neuroglycopenic signs were observed. The explanation of this phenomenon is not completely clear. Several factors
Glucose and gluoregulatory hormones on a control day (●–●) and after octreotide (○–○) (50 μg sc at 08.00 h, interrupted line) in 2 patients with insulinoma. Meals were taken at 08.15 and 10.00 h.
Fig. 2.
Glucose and glucoregulatory hormones after octreotide (50 μg at 08.00 h, interrupted line) in a patient with insulinoma. •—• breakfast at 08.15 h; ○—○ breakfast at 07.45 h; ▲—▲ breakfast at 08.15 h with glucagon replacement from 08.10 to 10.00 h.
may be important. Firstly, both the natural somatostatin (8–11) and octreotide (12,13) have been shown to delay intestinal absorption of nutrients. This may have allowed hypoglycemia to develop when octreotide was administered before breakfast. This hypothesis was tested in patient B. A transient decrease in serum glucose after octreotide was absent after glucagon substitution, but present when breakfast was taken before administration of octreotide. Glucagon replacement has been shown to be unable to reverse the delay of carbohydrate absorption induced by somatostatin (8). An octreotide-induced delay of carbohydrate absorption, even if present, thus cannot explain these observations.

Secondly, both the natural somatostatin and its analogue octreotide are known to be able to suppress glucagon secretion (14–16). This conceivably could lower glucose levels. In favour of this hypothesis we observed a clear decrease in glucagon levels, which was in fact more rapid than the octreotide-induced suppression of insulin levels. The glucagon replacement experiment in patient B also appears to support this interpretation, provided that the glucagon levels obtained were physiological. The glucagon infusion rate chosen was based on a reported metabolic clearance rate of approximately 11 ml·kg⁻¹·min⁻¹ (17) and a portal: peripheral venous ratio of 2.7 (18). Glucagon levels averaged approximately 110 ng/l during the infusion compared with approximately 30 ng/l at baseline. The resultant ratio of 3.7 is higher than the reported portal: peripheral venous ratio of 2.7 and it therefore appears unlikely that portal venous glucagon levels during the replacement infusion were too low. The absence of a rapid and steep rise in glucose levels argues against the possibility that the glucagon levels were unphysiologically high.

Glucagon influences blood glucose mainly by regulation of hepatic glucose production (19). Indeed it appears that the octreotide-associated changes in blood glucose levels observed can be explained by rapid changes in hepatic glucose production, assuming a relatively constant rate of peripheral glucose utilisation. In addition, chronic hyperglucagonemia may increase intestinal carbohydrate absorption (20). For two reasons, however, this cannot explain the observed changes in blood glucose. Firstly, glucagon replacement cannot reverse somatostatin-induced reductions of nutrient absorption (8). Secondly, blood glucose levels in patient B continued to rise despite the fall in glucagon levels when octreotide was administered after breakfast.

Enhancement of peripheral glucose utilisation by somatostatin should also be considered as a cause of hypoglycemia. Our study was not designed to address this question, but in view of recent conflicting reports (21,22) this possibility cannot at present be excluded. Finally, the intrinsic sensitivity of the insulin-producing tumour with regard to the effects of octreotide may be an important determinant of the time course of the changes in blood glucose levels after administration of octreotide. The effectiveness of octreotide therapy in patients with hormone-producing gastrointestinal tumours appears to be mainly dependent on the number and affinity of somatostatin receptors on these tumours. A recent study found somatostatin receptors in two of five insulinomas (23). Lamberts (24) observed acute hypoglycemia after administration of octreotide in one patient whose insulinoma had receptors with high affinity for somatostatin-28 but low affinity for an octreotide derivative. Tumorous hypersecretion of insulin was not affected (in contrast to in our patients), but release of glucagon and growth hormone was suppressed, and glucose absorption from the gut was delayed.

In patients with insulinoma, the octreotide-associated decrease in glucose levels can provoke hypoglycemic symptoms. Furthermore, in this situation octreotide, like its parent peptide, may modify counterregulatory hormone secretion. Both the native somatostatin (25,26) and octreotide (27) have been shown to be able to suppress the glucagon and GH, but not the cortisol or catecholamine response to insulin-induced hypoglycemia. The results of our study are in agreement with these reports (25–27) except for the interesting finding of an octreotide-associated attenuation of the catecholamine response to hypoglycemia in patient A. This observation, if confirmed, would have important clinical implications, because some patients in whom octreotide therapy might be considered (e.g. with insulin-dependent diabetes) may be at increased risk for severe hypoglycemia in view of the marked attenuation of major defense mechanisms (i.e. the glucagon and catecholamine response).

This study shows that in patients with an insulin-secreting tumour, treatment with the long-
acting somatostatin analogue octreotide may be associated with a transient decrease in serum glucose levels. This may result in clinically important hypoglycemia. Furthermore, during hypoglycemia counterregulatory hormone secretion may be attenuated.

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References


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