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SMS 201-995 (Sandoz Pharmaceuticals, East Hanover, NJ) is a synthetic peptide analog of native somatostatin that has been used to relieve symptoms caused by neuroendocrine tumors. Reports have described an insulin suppressive effect of SMS 201-995 that results in elevations of blood glucose. We report a patient with a metastatic small bowel carcinoid and renal failure in whom mild symptomatic hypoglycemia occurred 30 to 60 minutes after SMS 201-995 administration. No increase in insulin or decreases in glucagon, cortisol, or catecholamines were observed during these hypoglycemic episodes. Elevated levels of growth hormone fell gradually following SMS 201-995 administration and did not temporally correspond to the 30- to 60-minute nadir of blood glucose. However, SMS 201-995 levels peaked during this 30- to 60-minute period. As clinical experience with this drug broadens, patients whose glucose control is dependent on counter-regulatory hormones should be monitored for the possibility of hypoglycemia. (Henry Ford Hosp Med J 1989;37:60-2)

Native somatostatin is a peptide hormone that inhibits multiple endogenous peptides and ectopic hormone secretion from neuroendocrine tumors. Its clinical usefulness is limited by its 3 minute half-life and the need for continuous intravenous infusion. SMS 201-995 (Sandoz Pharmaceuticals, East Hanover, NJ) is a synthetic octapeptide which can be administered by subcutaneous injection and has a prolonged duration of action (1). It has been successfully used to relieve symptoms in patients with refractory diarrhea due to the carcinoid syndrome (2). A side effect of SMS 201-995 is impaired glucose tolerance secondary to insulin suppression (3,4). We report a patient with metastatic small bowel carcinoid who experienced reproducible mild hypoglycemia after acute administration of SMS 201-995.

Subject

A 65-year-old black female (38.6 kg [85 lb]) with metastatic small bowel carcinoid, malnutrition, and dialysis-dependent end stage renal disease was admitted to our clinical research unit for treatment of her refractory diarrhea with SMS 201-995. Informed consent was obtained from the patient.

A pretreatment profile was obtained after an 8-hour overnight fast. Measurements of blood glucose, serotonin, insulin, and growth hormone were collected at −15, 0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes. A repeat study of blood glucose without SMS 201-995 was also obtained four months later.

Doses of 100 and 200 μg of SMS 201-995 were administered subcutaneously in the fasting state. Measurements of blood glucose, SMS 201-995, growth hormone, growth hormone-releasing hormone (GHRH), catecholamines, glucagon, cortisol, and serotonin were collected at the same intervals as in the pretreatment day.

Daily therapy consisted initially of 50 μg subcutaneously twice a day and was gradually increased to 150 μg subcutaneously three times a day over a total of 12 weeks.

Methods

Tissue blocks from the original tumor resection were studied in a biotin-avidin-immunoperoxidase system with antibodies for growth hormone, GHRH, serotonin, and pancreatic polypeptide.

Radioimmunoassay (RIA) measurements for SMS 201-995, pancreatic polypeptide, and glucagon levels were performed by

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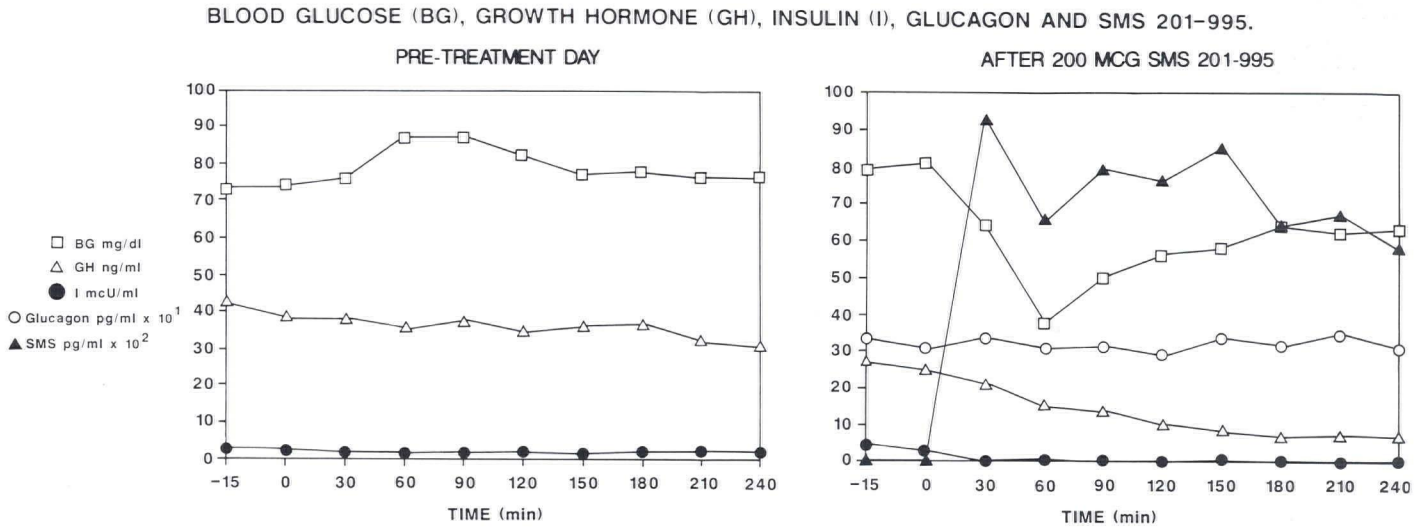

Figure—Left panel: Fasting blood glucose (BG), growth hormone (GH), and insulin (I) without SMS 201-995 during a 240-minute period of observation. Right panel: Blood glucose, growth hormone, insulin, SMS 201-995, and glucagon after a single subcutaneous injection of 200 μg of SMS 201-995 at time 0.

Dr. Thomas O'Dorisio, Ohio State University, Columbus, OH. GHRH assays were performed by Dr. Lawrence Frohman, University of Cincinnati. Growth hormone was measured with the Quantitope HGH kit (Kallestad Diagnostics, Austin, TX). Insulin was measured by RIA. Somatomedin C was measured by the Nichols Institute (San Juan Capistrano, CA). Serotonin levels were collected in tubes containing EDTA and ascorbic acid and measured by Smith Kline Bio-Science Laboratories (Van Nuys, CA) by a fluorometric method. Blood glucose was measured with a YSI model 23A glucose analyzer (Yellow Springs, OH). Plasma catecholamines were measured by high-pressure liquid chromatography.

Results

In two baseline studies without SMS 201-995, the blood glucose remained stable over 240 minutes (Figure [left panel]). During three separate challenges with SMS 201-995, blood glucose began to fall by 30 minutes and reached a nadir at 60 minutes of 47, 44, and 38 mg/dL, respectively (Figure [right panel]). During these episodes of blood glucose reduction, the patient experienced sensations of weakness, hunger, tachycardia, and sweats that resolved spontaneously. This symptomatic hypoglycemia occurred at peak SMS 201-995 levels (Figure [right]). Insulin levels remained under 4 μU/mL at all times. Glucagon remained elevated (mean ± SD = 323 ± 17.1 pg/mL) and did not change during the 240-minute observation period after SMS 201-995 administration. Cortisol did not fall, and catecholamines remained stable until 60 minutes when they rose above baseline values, presumably in response to hypoglycemia.

A fasting growth hormone level of 42 ng/mL was higher than we had expected. Evaluation of the tumor with immunoperoxidase staining revealed only serotonin immunoreactivity. The patient had no somatic features of acromegaly. Somatomedin C levels were normal at 1.5 U/mL (normal = 0.45 to 2.2 U/mL), and GHRH was not elevated at 18.7 pg/mL (normal = < 25 pg/mL). In the pretreatment state, a gradual spontaneous 29% reduction in growth hormone occurred over 240 minutes (Figure [left]). In response to SMS 201-995, there was a gradual 72% reduction in growth hormone over the 240-minute observation period (Figure [right]) with no discernible nadir correlating with the nadir in blood glucose.

During chronic analog treatment, no decrease in diarrhea occurred and plasma serotonin levels were unchanged. In the fed state the patient reported no symptomatic episodes of hypoglycemia.

Discussion

The purpose of treatment with SMS 201-995 in this patient was to decrease her diarrhea and possibly promote tumor regression. Neither of these responses was observed. The inability to reduce stool volume may have been due to a short bowel syndrome from previous intestinal resections and a lack of tumor receptors for somatostatin.

The anticipated response to SMS 201-995 is a rise in blood glucose due to the insulin suppressive effect of the analog (3-6). The reduction in blood glucose which we observed may occur through several mechanisms. For example, in type 1 insulin-dependent diabetes mellitus, reductions in postprandial blood glucose have been described with the administration of somatostatin analogs and native somatostatin (7,8). This has been explained by the inhibitory effects of somatostatin on glucagon and on bowel nutrient absorption (7,8). Infusions of

native somatostatin have also been used to lower the blood glucose in diabetic ketoacidosis where large elevations in glucagon and growth hormone are thought to contribute to the hyperglycemia and ketogenesis (9). However, we did not observe a reduction in glucagon (Figure [right]), and insulin remained suppressed throughout all studies.

Patients with multiple liver metastasis, renal failure, and malabsorption and malnutrition due to diarrhea are subject to symptomatic hypoglycemia due to reduced glycogen stores and impaired gluconeogenic processes (10). Maintenance of adequate blood glucose levels in the fasting state requires counter-regulatory elevations in growth hormone and glucagon. Inhibition of growth hormone by SMS 201-995 may have caused blood glucose to decline. However, the reduction in growth hormone did not temporally parallel the glucose nadir during the 30- to 60-minute period. Another possible mechanism for the decrease in blood glucose may have been the inhibition of bowel nutrient absorption, but this patient's diarrhea, rapid gastrointestinal transit time, and fasting state should have minimized this effect.

Temporally, SMS 201-995 was peaking during the 30- to 60-minute period when blood glucose was reaching its nadir. An insulin-like action of SMS 201-995 or suppression of another unknown glucose regulating process could explain this phenomenon.

Hypoglycemia did not occur if the analog was administered after the patient had been fed. Other patients whose glucose homeostasis may be tenuous or dependent on counter-regulatory hormones should be monitored for hypoglycemia after administration of SMS 201-995 in the fasting state.

Acknowledgment

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