# Somatostatin Analogue (SMS 201-995) in the Management of Gastroenteropancreatic Tumors and Diarrhea Syndromes

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**SMS 201-995 (Sandostatin) was studied using low doses (50 to 100 μg) administered subcutaneously every 12 hours. A single 50-μg dose of SMS 201-995 effectively controlled gastric acid and blood gastrin levels for 12 hours in three patients with benign gastrinomas and was useful in their perioperative management. Higher doses of the agent (500 to 800 μg per day) had no effect on metastases in one of two patients with metastatic gastrinoma. In the other patient, one tumor shrank but the other continued to grow after three months of treatment while serum gastrin levels did not change. Cultured metastatic tumor tissue from this patient released different forms of gastrin; growth rates varied, independent of uptake of SMS 201-995, and gastrin release increased. A neonate with nesidioblastosis maintained normal blood glucose levels while receiving SMS 201-995 therapy following a 95 percent pancreatic resection. In two elderly patients with organic hypoglycemia—one with a single benign adenoma and one with multiple adenomatosis—the somatostatin analogue did not prolong the hypoglycemia-free interval. In nine patients with carcinoid syndrome, flushing was uniformly controlled with 50 μg of SMS 201-995 administered every eight to 12 hours. One of the nine required exocrine pancreatic replacement. After six months of treatment, three of the nine had no change in tumor size and one had remission of symptoms and stopped treatment. In two patients with vipoma, SMS 201-995 controlled diarrhea and reduced levels of vasoactive intestinal peptide; tumor necrosis occurred in one patient. In a patient with diabetic diarrhea unresponsive to all treatments, SMS 201-995 therapy controlled the diarrhea but did not interfere with control of the diabetes.**

Neuroendocrine tumors of the gastroenteropancreatic axis (e.g., gastrinoma, insulinoma, somatostatinoma, vipoma, and ppoma, among others) are more frequently recognized now that their clinical features are better known and diagnostic methods have improved [1]. Although more than 35 peptides are produced in the gastroenteropancreatic axis, only six clinical manifestations of hormone excess are currently recognized: peptic ulcers, diarrhea, dermatosis, diabetes, hypoglycemia, and flushing [2]. Neuroendocrine tumors may be clinically silent but secrete gastroenteropancreatic hormones, such as pancreatic polypeptide, that show little biologic activity [1,2]. Many of these syndromes are amenable to surgical or medical treatment [1,2]. Surgical treatment, directed toward the target organ (e.g., the stomach in gastrinoma syndrome), increases life expectancy. Early removal of the tumor may prevent death from tumor metastases [3]. However, in some patients, the tumor cannot be removed and

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Sandostatin (octreotide) is a registered trademark of Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey. Sandostatin is also known as SMS 201-995, SMS, and somatostatin analogue.

available medical therapy for the symptom complex is inadequate.

The advent of histamine $H_2$-receptor antagonists revolutionized the management of gastrinoma syndrome [4], obviating the need for total gastrectomy in most cases [4–6]. However, in 15 to 30 percent of patients, these drugs are not effective initially or ultimately fail [7,8]; thus, more potent antisecretory agents are being sought. In addition to controlling acid secretion, methods to treat the tumor are now being investigated since the incidence of gastrinoma metastases is between 60 and 90 percent [4,5,9], and 20 percent of patients die of metastatic disease [10].

In experimental animal and human studies, native somatostatin-14 was found to inhibit gastric secretion [11–14]; however, since its biologic half-life is short [15], it must be given continuously. Preliminary results with the long-acting somatostatin analogue SMS 201-995 in the management of gastric acid hypersecretion have been encouraging [16,17], and the drug may have potential as an anti-tumor agent in certain gastroenteropancreatic endocrine tumors [17–19].

Organic hypoglycemia with hyperinsulinism is a relatively rare but well-described [20] syndrome that includes several pathologic states of the endocrine pancreas. The pathology dictates the type of therapy selected to prevent hypoglycemia and control hyperinsulinism if possible. Surgery is preferable for single adenomas because of the high cure rate. When surgery is not possible, medical management includes phenytoin [21,22], diazoxide, thiazide diuretics [23,24], and beta blockers [25–27] to suppress insulin release, but none of these is ideal and all are associated with significant side effects. These modalities, along with tumoricidal agents such as streptozotocin [28,29], 5-fluorouracil [30], and doxorubicin [31], are used to treat malignant insulinomas; the results are variable and the tumors may become refractory to these drugs.

The carcinoid syndrome was recognized more than 75 years ago, but the spectrum of amines and peptides produced by these tumors is only now being explored. Carcinoids are heterogeneous, multipotential lesions that are important in the pathogenesis of one or more symptoms, and are, therefore, markers of actively secreting tumors. The characteristic features of the carcinoid syndrome include facial flushing, diarrhea, dyspnea on exertion, and bronchial spasm. The presence of a carcinoid tumor correlates with serum or plasma serotonin levels.

Flushing, a transient reddening of the face and frequently the neck, upper chest, and epigastric area, is often the initial manifestation of endocrine tumors [1], notably carcinoid [32,33], but also pheochromocytoma [34] and medullary carcinoma of the thyroid [35]. A variety of vasoactive substances produced by carcinoids, including serotonin [36], catecholamines [1], prostaglandins [37], calcitonin [38], vasoactive intestinal peptide [39], substance P [40], and motilin [41] cause the classic intermittent episodes of flushing that are biochemically and pharmacologicly heterogeneous [42].

Surgery to resect the tumor is the therapy of choice when the diagnosis can be confirmed and the tumor localized. When surgery is not possible, an accurate biochemical and hormonal diagnosis is the key to rational medical treatment. However, management of patients who do not have distinct biochemical or hormonal abnormalities, or whose condition is refractory to standard treatment, is difficult. Somatostatin and its analogues have been reported to block the spontaneous and pentagastrin-provoked episodes of flushing in patients with carcinoid syndrome [43,44].

Diarrhea may be a prominent symptom in patients with carcinoid syndrome, medullary carcinoma of the thyroid, gastrinoma syndrome, and the vipoma syndrome. The mechanisms responsible for the diarrhea appear to be quite different for these conditions [1,2]. In the gastrinoma syndrome, it appears to be gastric acid hypersecretion with damage to the small intestine mucosa, inactivation of enzymes, and precipitation of bile salts. The diarrhea of the gastrinoma syndrome is unique in that it responds to $H_2$-receptor blocking drugs; however, symptomatic control may not be achieved in all patients. In the other conditions, the diarrhea is usually secretory, will not disappear with fasting, and causes a net secretion of fluid and electrolytes, confirmed by small bowel secretion studies. The agents used to manage secretory diarrhea produce variable results [2].

The "diabetic diarrhea" seen in patients with labile, poorly controlled, long-term, insulin-requiring or insulin-dependent diabetes coexisting with peripheral and/or autonomic neuropathy occasionally responds to treatment with antidiarrheal agents, antimicrobial agents, pancreatic enzyme, bile acid exchange resin, and clonidine, given alone, or in combinations [45–47].

The effect of SMS 201-995 on diarrhea refractory to all forms of therapy in a variety of endocrine tumors and in a patient with insulin-dependent diabetes is reported.

## GASTRINOMA SYNDROME

The clinical details of five patients with gastrinoma syndrome are summarized in **Table I**.

**Benign.** Patients 1, 2, and 3 had hypergastrinemic hyperchlorhydria and benign gastrinomas, one in the duodenal wall, one in a peripancreatic lymph node, and one within the liver, localized preoperatively by percutaneous transhepatic venous sampling [3]. Their gastric acid secretory response to various forms of treatment was studied. After an overnight fast and withdrawal of $H_2$-blockers and other antisecretory agents for 24 hours, a nasogastric tube was placed in the stomach (its position was con-

**TABLE I Clinical Features of Five Patients with Gastrinoma Syndrome**

| Case Number | Age (years) | Sex | Symptoms/Duration | Tumor | Basal Acid Output/ Maximal Acid Output (meq/hour) | Secretin Test | | Prior Treatments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Basal Gastrin | Peak (pg/ml) | |
| 1 | 61 | F | Diarrhea, weight loss (3 months) | Duodenal wall | 43/38 | 436 | 652 | Ranitidine 600 mg/day<br>Probanthine 60 mg/day |
| 2 | 55 | M | Nausea, vomiting, ulcer disease, bleeding (10 years) | Peripancreatic lymph node | 44/48 | 73 | 189 | Cimetidine 4,200 mg/day<br>Ranitidine 1,200 mg/day<br>Probanthine 75 mg/day<br>Exploratory laparotomy |
| 3 | 43 | M | Diarrhea (2 years) | Liver | 31/24 | 455 | 2,159 | Ranitidine 3,600 mg/day<br>Probanthine 45 mg/day |
| 4 | 38 | M | Abdominal pain, weight loss, ulcer disease (6 years) | Metastatic | 31/– | 17,497 | 24,840 | Total gastrectomy<br>Partial pancreatectomy<br>Chemotherapy (5-fluorouracil, streptozotocin, fluorodeoxyuridine, BCNU, doxorubicin, mitomycin-C) |
| 5 | 58 | M | Diarrhea (5 years) | Metastatic | 26/31 | 6,704 | 7,046 | Total gastrectomy<br>Partial pancreatectomy<br>Chemotherapy (5-fluorouracil, streptozotocin, fluorodeoxyuridine)<br>Radiation |

BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea, carmustine.

firmed fluoroscopically), and gastric aspiration was achieved by continuous suction using a negative pressure pump.

Using a crossover design, the three patients were randomly given subcutaneous injections of SMS 201-995, 50 to 100 μg per day, every six to 12 hours for up to 48 hours, followed by a 24-hour washout period, and then either normal saline or cimetidine, 200 to 1,200 mg intravenously, every four to six hours for 12 to 48 hours. Gastric juice and blood samples were collected during a four-hour baseline period, and at four-hour intervals during administration of the study agents.

The gastric secretory response to the treatment regimens was similar in the three patients (**Figure 1**). In contrast to either normal saline or cimetidine, SMS 201-995 lowered serum gastrin and reduced gastric acid secretion; the response was dose-related, with a greater response to 100 μg given every six hours than to 50 μg given every 12 hours. In Patient 1, who received 100 μg of the somatostatin analogue every six hours, gastric secretion was completely inhibited eight hours after the first injection: gastric pH rose from 1.2 to 7.6, acid output dropped to zero, gastric secretory volume decreased comparably, and the patient's gastrin level returned to normal.

Patients 1 and 2 received 50 μg of SMS 201-995 subcutaneously on the morning of their surgical procedure to suppress gastric acid secretion and to counteract the loss of large volumes of acid and severe metabolic alkalosis resulting from continuous gastric aspiration. In Patient 2, a postoperative rebound in gastric acid secretion occurred despite continued administration of the analogue, 50 μg every six hours. However, increasing the dose resulted in a significant reduction in the daily volume of gastric aspirate over six days; the patient showed marked improvement and oral feeding was resumed.

In Patient 3, one 100-μg subcutaneous injection of SMS 201-995 markedly reduced blood flow to the tumor (**Figure 2**), and within 15 minutes right hepatic vein gastrin decreased to normal levels.

**Metastatic.** Patients 4 and 5 had hepatic metastases from an unidentified primary focus. Each had had a total gastrectomy, partial pancreatectomy, and chemotherapy, but both showed clinical and radiologic evidence of progressive tumor enlargement. They were entered into our study protocol for three to six months, and were followed clinically at two- to four-week intervals for routine biochemistry and serum gastrin determinations. Computerized axial tomographic scans (CT scans) were obtained every three months.

In Patients 4 and 5, blood samples for gastrin were obtained every four hours, starting eight hours before and continuing for 48 to 96 hours, for each SMS 201-995 dosage used. Dosage was titrated over three to six months based on serum gastrin levels, with normal gastrin levels as the clinical goal. Only a modest decline in gastrin levels for up to 12 hours occurred following the short-term suppression test with SMS 201-995.

During the initial three months of therapy, Patient 4 re-

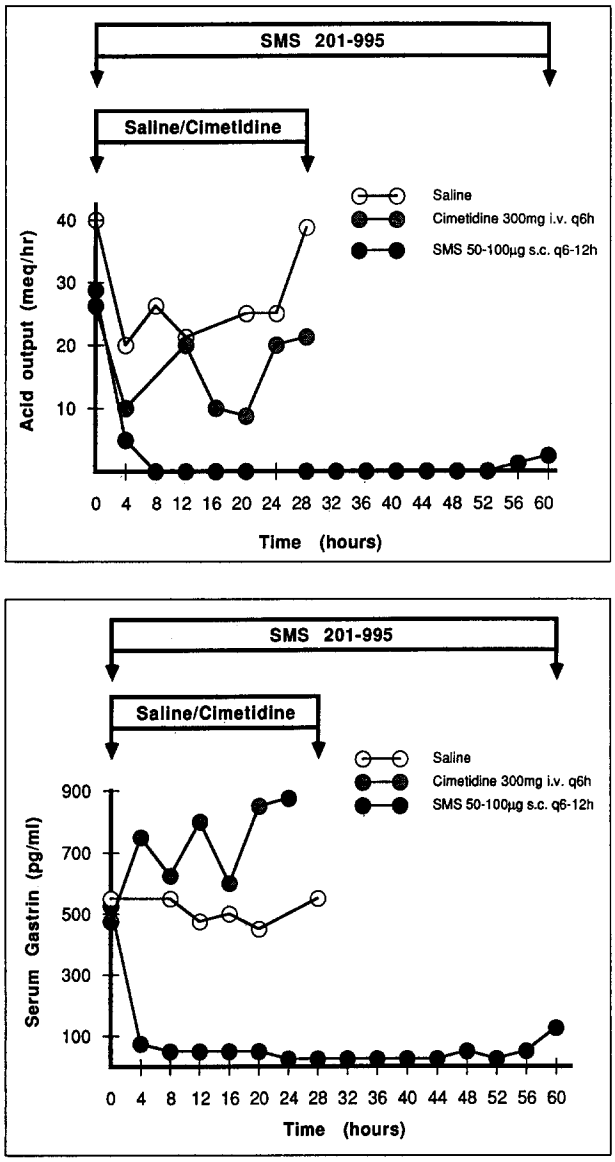


***Figure 1.*** *Gastric acid responses (acid output,* ***top;*** *serum gastrin,* ***bottom****) to saline, cimetidine, and SMS 201-995 in patients with benign gastrinoma.*

ported feeling better; but even with increasing doses, serum gastrin levels did not return to normal. At the end of three months, a left lobe hepatic metastasis was found to be growing ("big tumor"), while another metastatic tumor in the right lobe was regressing ("small tumor"). The two tumors were resected and therapy with SMS 201-995 was continued perioperatively. Portions of the two tumors were extracted as previously described [48] to determine gastrin, somatostatin, and SMS 201-995 content. Somatostatin analogue content was determined by a recently described radioimmunoassay from the laboratory of Dr. Thomas M. O'Dorisio at the Ohio State University. This assay has been shown to be non-cross-reactive with endogenous native somatostatin [49].

Five hours after subcutaneous administration of 100 μg of SMS 201-995, the drug concentration in the "big tumor" was 126 ng/g net weight. The analogue's concentration in the "small tumor" was 72 ng/g net weight six hours after the injection. Results of in vitro studies of these tumors with and without SMS 201-995 are shown in **Table II**. Increasing concentrations of the analogue, from 0.5 to 5 μg/ml, paradoxically increased the gastrin content in the media for the "big tumor" at all doses. In the "small tumor," gastrin decreased slightly with 5.0 μg/ml of SMS 201-995. On chromatographic analysis of extracted gastrin, the predominant form was gastrin-17 in the "big tumor" and gastrin-34 in the "small tumor."

Over six months, progressive enlargement of hepatic metastases occurred in Patient 5, who was treated with up to 500 μg of SMS 201-995 per day, but CT scans showed progressive enlargement of hepatic metastases (**Figure 3**). Cytotoxic treatment was reinstituted.

## HYPERINSULINISM

**Benign Insulinomas.** Patient 1 (TS) is a 33-year-old man who first experienced symptoms of symptomatic hypoglycemia in December 1982. In December 1984, during a second episode of hypoglycemia, his blood glucose was 21 mg/dl. Following a prolonged 14-hour fast, it dropped to 39 mg/dl. Immunoreactive insulin measured simultaneously was 26 μU/ml and the calculated insulin/glucose ratio was 0.7 (normal less than 0.3). Pertinent laboratory findings included a negative insulin antibody, a negative beta-human chorionic gonadotropin, and normal levels of prolactin, gastrin, and pancreatic polypeptide. CT scans of the abdomen were unremarkable. Mesenteric angiography disclosed a 3-cm vascular tumor in the isthmus of the pancreas.

Preoperatively, the patient fasted twice. During the first fast, no drug was given. During the second, 100 μg of SMS 201-995 was given subcutaneously every 12 hours. Plasma samples were obtained every four hours to measure levels of glucose, insulin, glucagon, proinsulin, and C-peptide. Immediately prior to surgery, the patient was given a subcutaneous injection of 50 μg of the analogue. His blood glucose was monitored intraoperatively. During surgery, his blood glucose was maintained at a mean of 161 ± 26 mg/dl without the aid of intravenous glucose. The immediate postoperative blood glucose value was 156 mg/dl.

During surgery, the body and tail of the pancreas were found to be normal. A 3-cm mass was found in the uncinate process of the pancreas, which was impinging on the duodenum. The tumor was difficult to enucleate cleanly, but was completely removed in a piecemeal fashion. Pancreatic ducts could not be identified in the tumor or in the remaining pancreatic tissue. Granules of immunoreactive insulin and serotonin were observed, but no

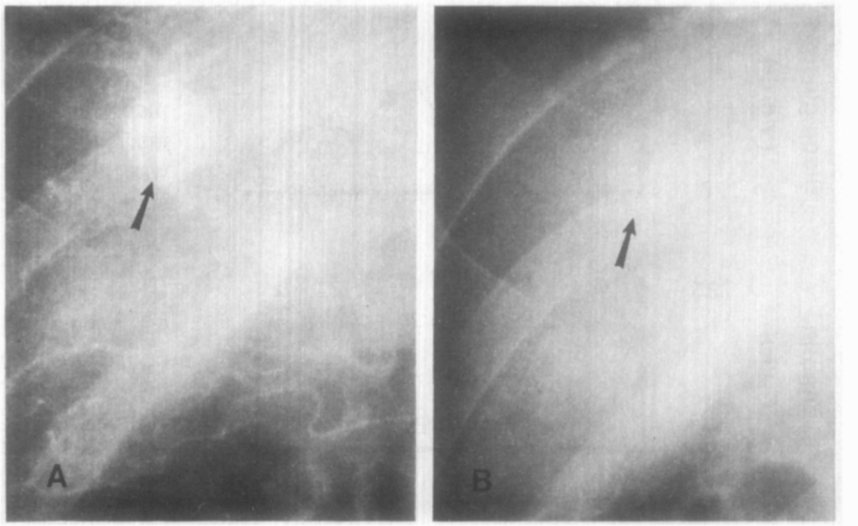


***Figure 2.*** *Responses of blood flow to an intrahepatic gastrinoma before (**A**) and after (**B**) the administration of SMS 201-995. **Arrows** indicate the tumor blush.*

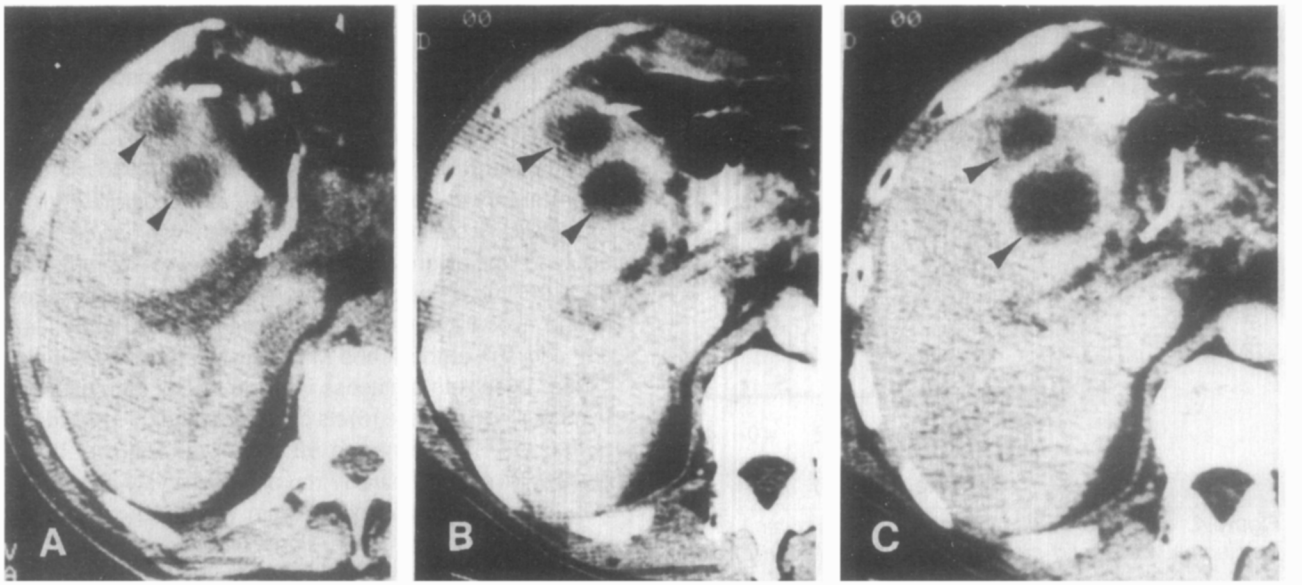


***Figure 3.*** *Computerized tomographic scans before (**A**) and after eight (**B**) and 11 (**C**) months of SMS 201-995 treatment showing progression of a metastatic gastrinoma.*

other gastrointestinal polypeptides were found by immunohistochemical staining.

Following surgery, symptomatic hypoglycemia developed in the patient, who had a measured blood glucose level of 41 mg/dl after fasting for 16 hours. After administration of 100 μg of SMS 201-995 every 12 hours, he was able to fast for 44 hours before becoming hypoglycemic, and his insulin level was suppressed to 25 percent of the basal value. C-peptide levels declined in parallel with the insulin levels. Glucagon dropped to one-third the fasting basal value, but rose towards baseline after 48 hours of treatment with the analogue (**Figure 4**).

Patient 2 (GL), a 59-year-old white woman, was admitted with a three-year history of hypoglycemic episodes. A previous workup revealed a vascular blush in the distal

**TABLE II Tumor Content of Somatostatin and SMS 201-995 and in Vitro Release of Gastrin**

| | Large Tumor | Small Tumor |
|---|---|---|
| Tumor content (ng/g tissue wet weight) | | |
| Somatostatin | 1.5 | 3.1 |
| SMS 201-995 | 126 | 72 |
| Release of gastrin (ng/g tissue wet weight/4 hours) | | |
| Without SMS 201-995 | 99 ± 18 | 424 ± 136 |
| With SMS 201-995 | | |
| 0.5 μg/ml | 210 | 344 |
| 2.5 μg/ml | 1,318 | 724 |
| 5.0 μg/ml | 1,710 | 2,333 |

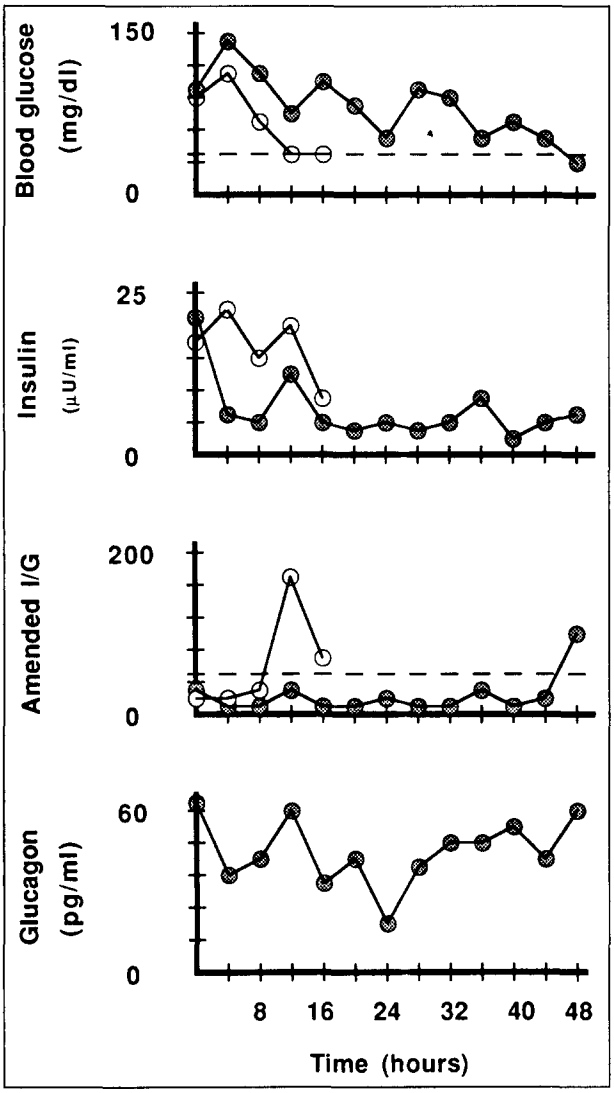


***Figure 4.*** *Effects of fasting in a patient with a benign single insulinoma with* ***(solid circles)*** *and without* ***(open circles)*** *SMS 201-995.*

pancreas consistent with an insulinoma. The patient was pretreated with SMS 201-995 and underwent resection of a 1.5 × 2 cm neoplasm in the distal pancreas under general anesthesia. The blood glucose and insulin responses in the perioperative period are shown in **Figure 5**.

Patient 3 (MP), an 82-year-old man, had a three-year history of episodes of sweating, palpitations, hunger, and mental confusion, which could be relieved by eating or drinking juice. He experienced episodes of uncontrolled motion of the arms and legs, clenched jaw, and occasional incontinence occurring between 3:00 and 6:00 A.M.; these symptoms could be prevented by eating every four to five hours. In October 1985, he had a fasting glucose level of 36 mg/dl and an insulin level of 38 μU/ml.

When admitted to the University of Michigan Hospital, he was in good health except for mild hypertension, atrial fibrillation, and some congestion at the bases of the lungs. In the preceding year, he had been treated for prostatic cancer with prostatectomy and 37 external radiation treatments. During this time, he had gained 10 pounds and his fasting glucose level was 36 mg/dl while his insulin level was 38 μU/ml. The fasting blood glucose level on admission was 40 mg/dl after a nine-hour fast, with an insulin value of 55 μU/ml, 55 percent of which was proinsulin. He perspired profusely and became quite confused. The results of both CT and (nuclear) magnetic resonance imaging (MRI) examinations were negative. A celiac axis angiogram and portal venous sampling indicated a tumor at the junction of the head and neck of the pancreas. A course of SMS 201-995 therapy had no effect on his blood glucose control. The drug was discontinued and diazoxide, 300 mg per day, and hydrochlorothiazide, 150 mg per day, were given; blood glucose levels improved and the interval between required food intake decreased from two to six hours (**Figure 6**). However, after 10 days on this regimen, he gained 18 pounds, incipient cardiac failure developed, and he was hospitalized. He underwent laparotomy and a benign adenoma at the junction of the head and neck of the pancreas was resected.

**Nesidioblastosis.** Hypoglycemia developed 40 minutes after delivery in Patient 4 (baby H), a male infant born at 37 weeks gestation by uncomplicated vaginal delivery. Glucose was given, but blood glucose levels ranged from 30 to 45 mg/dl, and he experienced recurrent seizures due to hypoglycemia. The infant was referred to Dr. Jeffrey Jackson at the A and M Medical Campus in Temple, Texas. Even with a glucose infusion rate of 22 mg/kg per minute, blood glucose levels dropped to the 35 to 50 mg/dl range. Insulin levels were 92 and 40 μU/ml with blood glucose levels of 16 and 17 mg/dl, respectively. Diazoxide was initiated 14 days postpartum but had no effect on blood glucose levels. The diagnosis of nesidioblastosis was made and the patient underwent 90 percent pancreatectomy on the 19th day.

During the postoperative period, blood glucose gradually declined to below 50 mg/dl necessitating glucose infusion, although the insulin level had fallen from 80 to 20 μU/ml. SMS 201-995 was started on Day 27, with an initial dose of 25 μg twice daily. Within the first five hours, a reduction in the glucose infusion rate was possible without hypoglycemia developing. The infusion was eventually stopped on Day 33 with blood glucose levels generally above 50 mg/dl. The insulin levels dropped to 13 μU/ml on Day 42 and finally to 8 μU/ml on Day 59. Oral feedings were started, but the patient had bouts of diarrhea, which were controlled by pancrelipase. He gained 1.5 pounds after starting therapy with the analogue and had a normal increase in body length and head circumference. His maintenance dose of SMS 201-995 is 30 μg twice daily (Jackson VA, et al: Treatment of refractory neonatal hypoglycemia and nesidioblastosis with a long-acting somato-

statin analogue [compound 201-995]. Presented at the International Conference on Somatostatin, Washington, DC, May 6–8, 1986).

**Multiple Adenomas.** Patient 5 (LW), a 72-year-old slightly overweight white woman with a history of non-insulin-dependent diabetes mellitus and hypertension for the past eight years, had been receiving 250 mg of chlorpropamide and hydrochlorothiazide daily until two months prior to her referral to the University of Michigan Hospital. She was referred because of a suspected episode of transient neurologic deficit early in the morning, followed two weeks later by a diagnosis of hypoglycemia based on a recent fainting spell at 3:00 A.M., at which time her blood glucose level was 38 mg/dl. Chlorpropamide had been discontinued four weeks earlier.

When evaluated, her blood glucose level was 34 mg/dl after a four-hour fast and 53 mg/dl after six to nine hours with an insulin level of 207 μU/ml; at 13 hours, the blood glucose level was 30 mg/dl with an insulin level of 128 μU/ml; and after 19 hours, the blood glucose level was 30 mg/dl with an insulin level of 154 μU/ml, and she was sweating profusely and had become disoriented. Proinsulin constituted 58 percent of the total insulin value (normal less than 22 percent) and CT and MRI examinations failed to disclose a tumor. A celiac axis angiogram showed two areas in the head and tail of the pancreas that were sus-

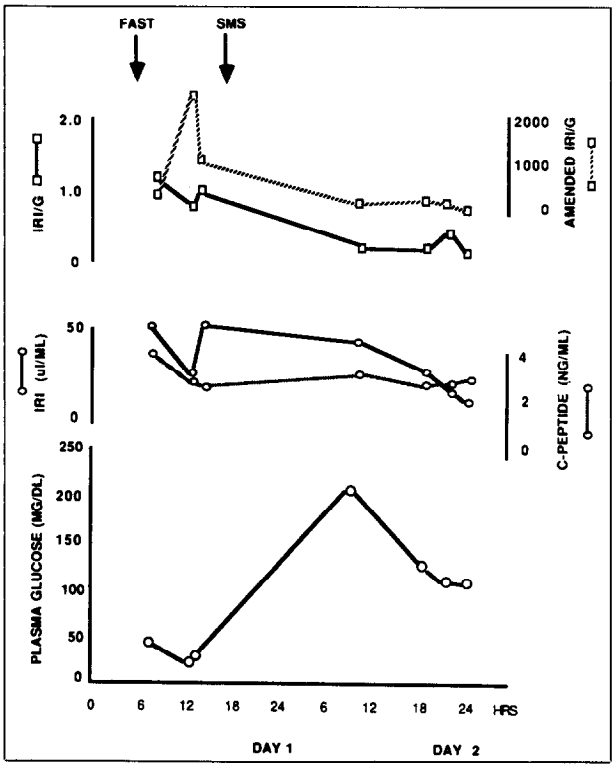


***Figure 5.*** *Successful use of SMS 201-995 in a patient with a single benign insulinoma.*

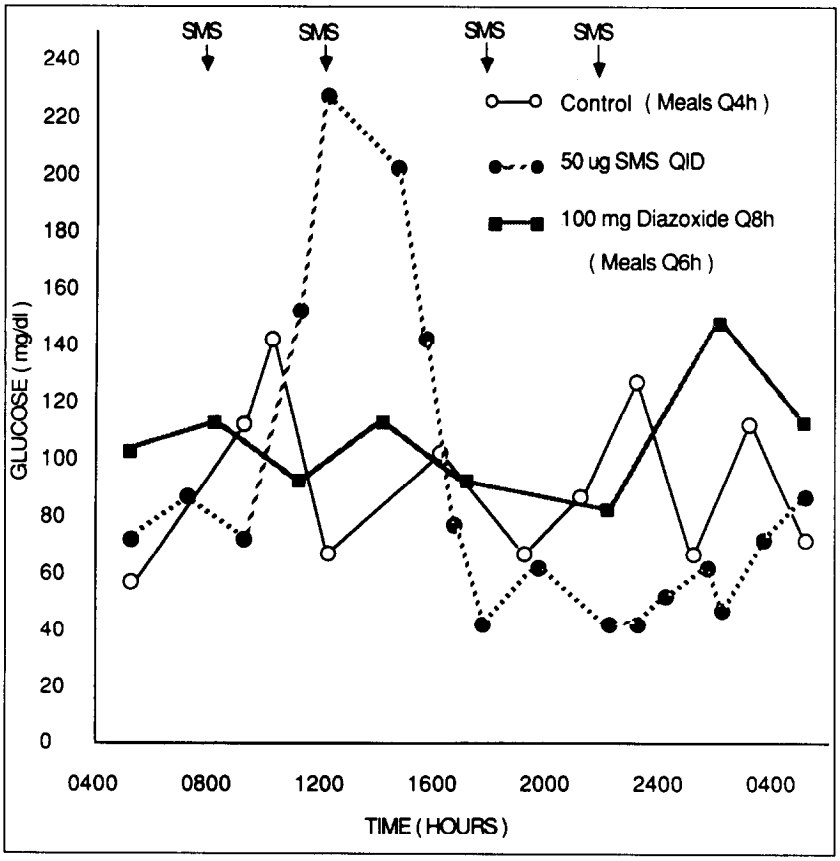


***Figure 6.*** *Twenty-four-hour glucose profile in a 82-year-old patient with a single benign insulinoma. Note that SMS 201-995 raised the blood glucose responses to the morning meal but failed to prevent later hypoglycemia, whereas diazoxide raised blood glucose levels throughout the day.*

pected of being tumors. Simultaneous transhepatic portal venous sampling confirmed the presence of at least two step-ups in the insulin concentration in the venous drainage areas of the head and tail of the pancreas. Three months later, a trial of SMS 201-995 therapy resulted in more severe hypoglycemia. The analogue was stopped and replaced with 200 mg of diazoxide per day and 150 mg of hydrochlorothiazide, which maintained euglycemia. After 10 days of treatment, anasarca and congestive cardiac failure developed and she was admitted to the hospital for definitive treatment of her organic hyperinsulinism.

## CARCINOID SYNDROME

At the University of Michigan, between 1959 and 1981, 35 cases of the carcinoid syndrome associated with carcinoid tumors were seen. Urine 5-hydroxyindoleacetic acid (5-HIAA) levels were abnormally elevated in 23 cases; all had metastases. Serum 5-hydroxytryptamine (serotonin) levels were found to be abnormally high in 26 patients. A rough correlation between the urinary level of 5-HIAA and tumor size was demonstrated.

Patient 1 (EP), a 58-year-old woman, presented with bowel obstruction. Laparotomy revealed a tumor in the small bowel causing obstruction and multiple enlarged mesenteric lymph nodes and liver lesions. Pathologic examination showed a multicentric carcinoid tumor with transmural invasion of the small bowel and metastasis to two of 10 mesenteric lymph nodes and to the liver. Following surgery, she underwent I-131 meta-iodo benzylguanidine scan to evaluate the possibility of radioisotope treatment, but the scan did not reveal liver or mesenteric metastases. A gastrointestinal hormone screen revealed elevated serotonin (1,125 ng/ml) and slightly elevated gastrin (158 pg/ml) levels. Subcutaneous injections of SMS 201-995, 50 $\mu$g twice daily, were started, and 10 months later the dosage was gradually increased to 150 $\mu$g twice daily without a significant drop in the serotonin level. Abdominal CT scans showed no change in size of the diffuse liver metastases.

Patient 2 (CS), a 61-year-old white man, was diagnosed as having carcinoid syndrome with metastases. He had repeated episodes of periumbilical pain with heme-positive stools but an upper and lower gastrointestinal series were negative. A CT scan of the abdomen showed a subpleural nodule in the lower lung field on the right and low attenuating lesions in the liver. Celiac axis angiogram indicated a vascular blush in the small bowel region. Urinary 5-HIAA levels were elevated. Laparotomy revealed a 6-cm mass in the distal ileal mesentery, which was resected along with three feet of bowel, and an end-to-end anastomosis was done. Multiple liver metastases were noted. Four months later, a hepatic artery pump was placed and five fluorodeoxyuridine treatments were given over four weeks. He continued to have intermittent diarrhea and repeated episodes of flushing, but no pulmonary hypertension and no increase in skin pigmentation developed. Telangiectasia occurred on the face, upper trunk, and forearms. The results of cardiac, pulmonary, and abdominal examinations were negative. Hemoglobin was 12.9 g/dl, alkaline phosphatase was 381 U/ml, and serotonin was 981 ng/ml (normal, 30 to 200 ng/ml); gut hormone levels were within normal limits.

Three months later, treatment was begun with SMS 201-995, 50 $\mu$g twice daily, and continued for three months; however, symptoms were not controlled and the dose was increased to 150 $\mu$g twice daily. After three months at the higher dose, serotonin levels fell to 211 ng/ml and symptoms virtually disappeared; however, after five months at the higher dose, the multiple hepatic metastases had not changed in size on CT examination.

Patient 3 (JB), a 58-year-old man with a diagnosis of carcinoid syndrome, had a two-year history of mild hypertension, diarrhea, and flushing spells and a 24-hour urinary 5-HIAA output of 78 mg (normal, 3 to 10 mg). Upper gastrointestinal endoscopy was unremarkable, but ultrasound revealed a large mass in the right lobe of the liver. Visceral angiography confirmed the presence of a hypervascular mass in the right lobe of the liver as well as multiple small masses scattered throughout the remainder of the liver. Laparotomy revealed a small primary tumor in the terminal ileum with significant involvement of the mesenteric nodes and a large secondary tumor in the liver. All were resected and found to be histologically compatible with carcinoid. The patient did well postoperatively, but after five months, flushing returned, one to two times every two to three days, and the frequency of watery stools increased. Treatment with SMS 201-995, 50 $\mu$g every eight hours, was started and an immediate improvement in diarrhea and flushing was noted. The tumor did not respond; serotonin was 981 ng/ml, the gut hormone profile was normal, and alkaline phosphatase was 381 IU/ml. Eight months later, the dose was increased to 150 $\mu$g every eight hours; after five months, the serotonin concentration fell to 211 IU and the alkaline phosphatase level to 217 IU/ml, but the liver tumor mass did not progress after 10 months of SMS 201-995 therapy (**Figure 7**).

## DIARRHEA

**Table III** illustrates the effect of a single 50-$\mu$g dose of SMS 201-995 on water and electrolyte transport in the small intestine in three patients with chronic diarrhea.

**Vipoma.** A 54-year-old woman was referred to the University of Michigan Hospital with a five-year history of refractory diarrhea and a 50-pound weight loss. She had required hospitalization several times for fluid and electrolyte imbalance resulting from uncontrollable diarrhea and vomiting. Fourteen months previously, a CT scan of the abdomen showed multiple liver metastases. Subsequent

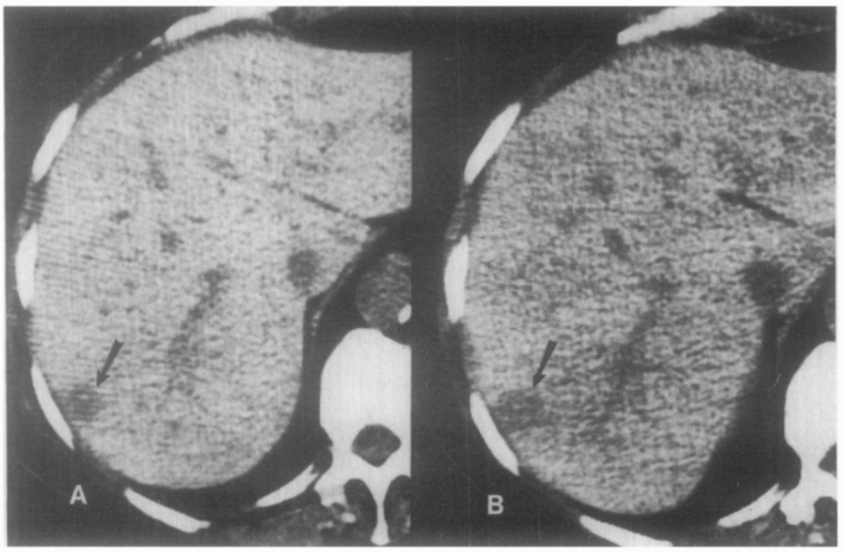


***Figure 7.*** *Arrest of progression of a hepatic metastasis from an appendiceal carcinoid metastatic to the liver after 10 months of treatment with SMS 201-995.*

**TABLE III Small Intestine Water and Electrolyte Movement in Three Patients with Chronic Diarrhea***

| Diagnosis | Water | Sodium | Chloride | Potassium | Bicarbonate |
|---|---|---|---|---|---|
| Vipoma | | | | | |
| −SMS | +51.0 ± 65.5 | +6.7 ± 9.6 | +7.8 ± 8.9 | −0.2 ± 0.2 | −1.0 ± 1.5 |
| +SMS† | −136.0 ± 46.6‡ | −20.0 ± 4.0‡ | −13.4 ± 3.9‡ | −0.9 ± 0.2‡ | −8.2 ± 0.8‡ |
| Substance Poma | | | | | |
| −SMS | −93.6 ± 41.3 | −12.4 ± 5.8 | −4.9 ± 3.7 | −0.8 ± 0.2 | −13.8 ± 12.6 |
| +SMS | −87.6 ± 40.2 | −12.8 ± 5.5 | −7.7 ± 4.9 | −0.7 ± 0.2 | −6.1 ± 0.9 |
| Diabetic enteropathy | | | | | |
| −SMS | −54.3 ± 49.7 | −8.0 ± 7.5 | −4.7 ± 6.2 | −0.2 ± 0.4 | NA |
| +SMS | −134.2 ± 60.1 | −15.8 ± 8.5 | −12.1 ± 6.7 | −0.7 ± 0.2 | NA |

NA = not applicable.
*Perfusate (isotonic solution): sodium, 140 mM; potassium, 5 mM; chloride, 110 mM; bicarbonate, 35 mM; pH 8.1; polyethylene glycol, 5 g/liter. Normal range: water, −15 to −115 ml/hour/30 cm; sodium, −4.1 to −16.5 meq/hour/30 cm; chloride, −0.4 to −14.7 meq/hour/30 cm; potassium, +0.2 to −0.7 meq/hour/30 cm; bicarbonate, −1.7 to −7.4 meq/hour/30 cm. Values are mean ± SE of three to five measurements; + = net secretion, − = net absorption.
†+SMS refers to response to subcutaneous administration of 100 μg of SMS 201-995 (Sandoz, Inc.)
‡$p < 0.05$.

liver biopsy eight months later suggested adenocarcinoma, and a five-month course of chemotherapy with 5-fluorouracil was initiated. Following chemotherapy, the findings of a repeat liver biopsy was consistent with carcinoid; plasma serotonin levels were normal. One month later, her plasma vasoactive intestinal peptide level was found to be markedly elevated (1,163 pg/ml; normal below 170 pg/ml) and the diagnosis of vipoma was made.

When admitted to the University of Michigan Hospital, she was cachectic and dehydrated. The liver was enlarged and had a hard irregular consistency. Liver and renal function were normal with moderate hypokalemia. Hormone values were as follows: vasoactive intestinal polypeptide, 688; gastrin, 91; somatostatin, 123; pancreatic polypeptide, 715 pg/ml; growth hormone, 11.9; prolactin, 27 ng/ml; parathyroid hormone midportion, 134, and N-terminal 14 ngeq/ml; and calcium, 11 mg/dl.

Her hospital course was complicated by watery diarrhea of up to 9 liters per day with marked hypokalemia and bicarbonate wasting. Intravenous hyperalimentation and subcutaneous administration of SMS 201-995, 100 μg per day, were initiated. The drug dose was gradually increased to 200 μg four times per day. The response to SMS 201-995 was impressive; bowel movements were reduced to one to two formed stools per day. Stool volume decreased to less than 500 ml per day, weight increased steadily, and potassium bicarbonate concentration returned to normal. CT scans showed massive tumor replacement of the liver. Treatment with the analogue, 200 μg four times per day, was continued for two months and then the dose was reduced to 100 μg four times per day. Levels of vasoactive intestinal polypeptide dropped to 160 pg/ml, those of pancreatic peptide to 186 pg/ml, and those of endogenous somatostatin to 18 pg/ml. She was readmitted two months after discharge with increasing abdominal pain and fever. Repeat CT scans (**Figure 8**) showed

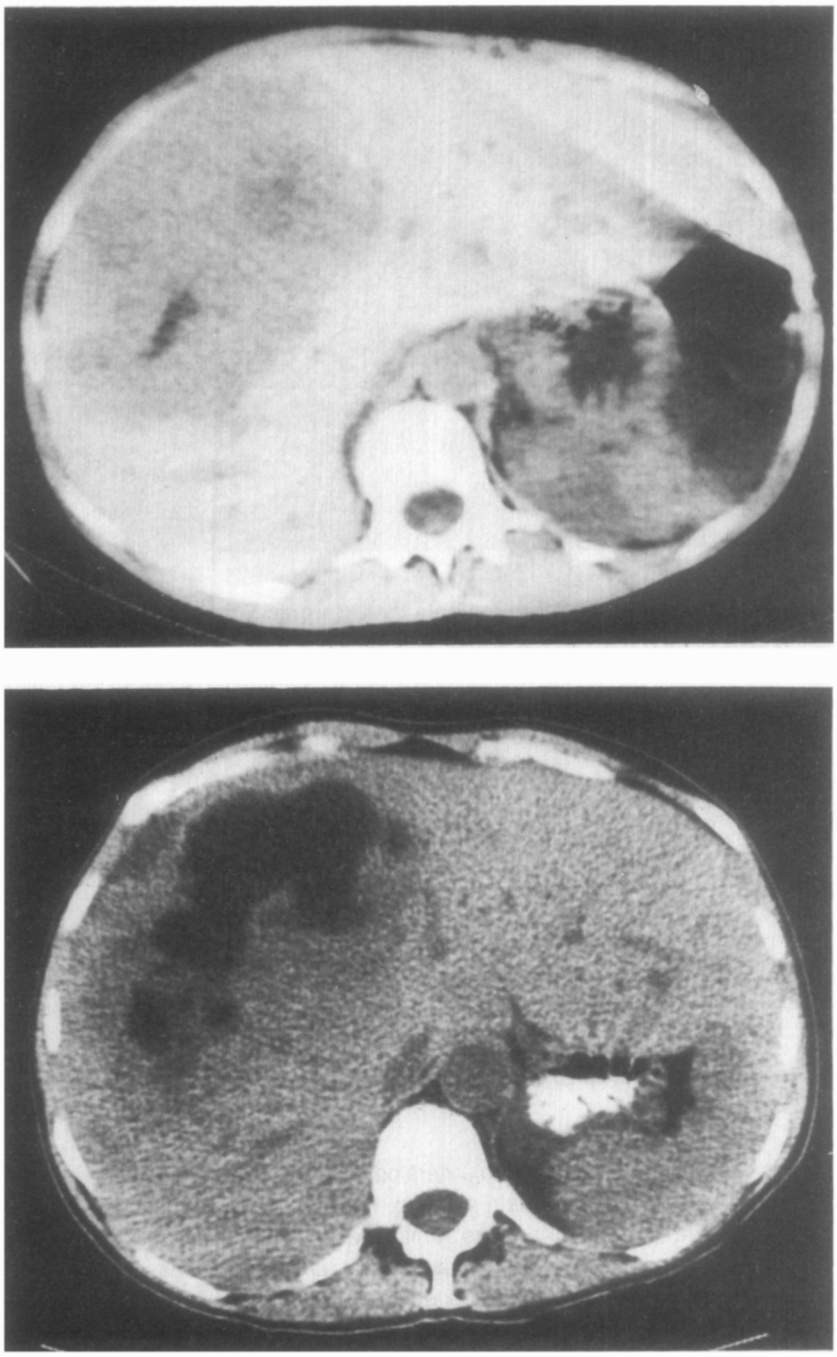

***Figure 8.*** *Vipoma metastatic to the liver before (**top**) and after (**bottom**) six months of treatment with SMS 201-995. The tumor appears to have undergone infarction.*

massive tumor necrosis. She underwent laparotomy and approximately 750 ml of necrotic tissue was evacuated from the liver and found to be histologically compatible with a neuroendocrine tumor. Gram-negative organisms were found in the necrotic tissue. Her postoperative recovery was uneventful, and she has no diarrhea. The most recent level of vasoactive intestinal polypeptide was 209 pg/ml (**Figure 9**).

We believe that the somatostatin analogue controlled the diarrhea, lowered hormone levels, and might have been responsible for infarction of the tumor. We suggest that SMS 201-995 might act directly to decrease tumor blood flow and that its use in patients with tumors refractory to conventional chemotherapy might be warranted.

**Diabetic Diarrhea.** A 39-year-old woman was admitted with progressive watery diarrhea unresponsive to treatment. She had a 17-year history of poorly controlled insulin-dependent diabetes mellitus complicated by retinopathy, nephropathy, peripheral and autonomic neuropa-

thies, and a below-the-knee amputation for vascular disease. Her autonomic neuropathy was manifested by postural hypotension, gastroparesis, and a neurogenic bladder. She had intermittent bouts of loose bowel movements for 10 years, which responded to antispasmodics and antidiarrheal agents. Fifteen months prior to admission, profuse, painless, watery diarrhea developed with an increased frequency of up to 15 times per day and a daily stool output of 5 to 6 liters. The explosive episodes of diarrhea prevented a normal social life. The stools were free of blood, pus, and mucus, and tests for occult blood, leukocytes, culture, ova, parasites, and laxatives were negative. Stool osmolality was 317 mOsm/kg, and 24-hour fecal fat was 62 g. She reported a 20-pound weight loss during the last year, but no history of foreign travel or laxative abuse. Treatment with diphenoxylate, loperamide, psyllium hydrophilic mucilloid, and pancrelipase failed to control the diarrhea. However, while maintained on central hyperalimentation and bowel rest, her stool volume declined to 400 to 600 ml per day, and she regained her previous weight.

Plasma concentrations of vasoactive intestinal polypeptide, motilin, somatostatin, serotonin, substance P, pancreatic polypeptide, and calcitonin were normal; the results of the secretin test (1,112 to 1,816 pg/ml) were positive, and basal hypergastrinemia (232 to 24,768 pg/ml) was present. Basal hypochlorhydria was unresponsive to betazole or pentagastrin. Serum gastrin was suppressed by continuous intragastric infusion of 0.1 N hydrochloric acid (1,385 to 593 pg/ml).

Findings on radiologic examination were normal except for the presence of retained gastric contents and some dilated loops of small bowel. Radionuclide study confirmed the clinical diagnosis of gastroparesis. A pancreatic function test showed decreased trypsin and lipase responses to stimulation by cholecystokinin. Hydrogen breath tests yielded abnormal findings in the basal state and after lactose challenge. The results of the Schilling and D-xylose tests were normal.

The patient consented to a trial of 50 $\mu$g of SMS 201-995 given twice daily, which was increased to 75 $\mu$g twice daily, given with her insulin injection 30 minutes before breakfast and dinner. On a regular diabetic diet plus Isotein, within 10 days of initiation of treatment with SMS 201-995, stools were semi-formed and stool volume was reduced to 400 to 800 ml per day. During the outpatient phase of the study, the patient monitored her blood sugar and stool frequency and character. During maintenance therapy with the analogue, bowel movements decreased to one or two per day; stools were usually semi-formed, diabetic control was stable, and the daily insulin requirement was essentially unchanged over a four-month follow-up period. The drug was well tolerated, and neither gastroparesis nor postural hypotension was aggravated (**Figure 10**).

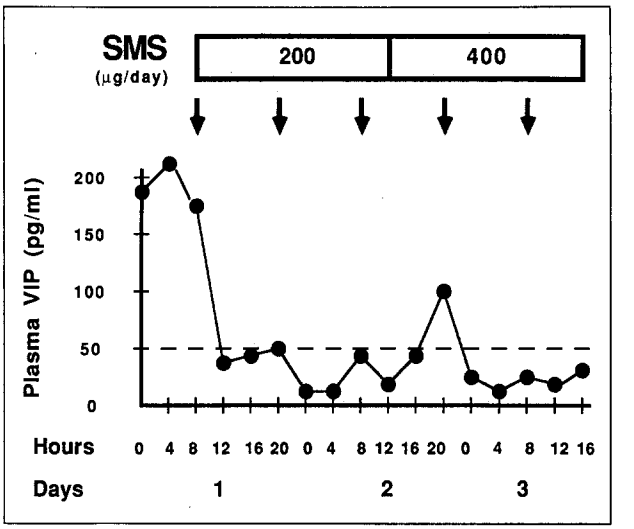


***Figure 9.*** *Responses of vasoactive intestinal peptide levels to treatment with SMS 201-995 in a patient with a metastatic vipoma. The decline in vasoactive intestinal peptide levels coincided with a disappearance in diarrhea.*

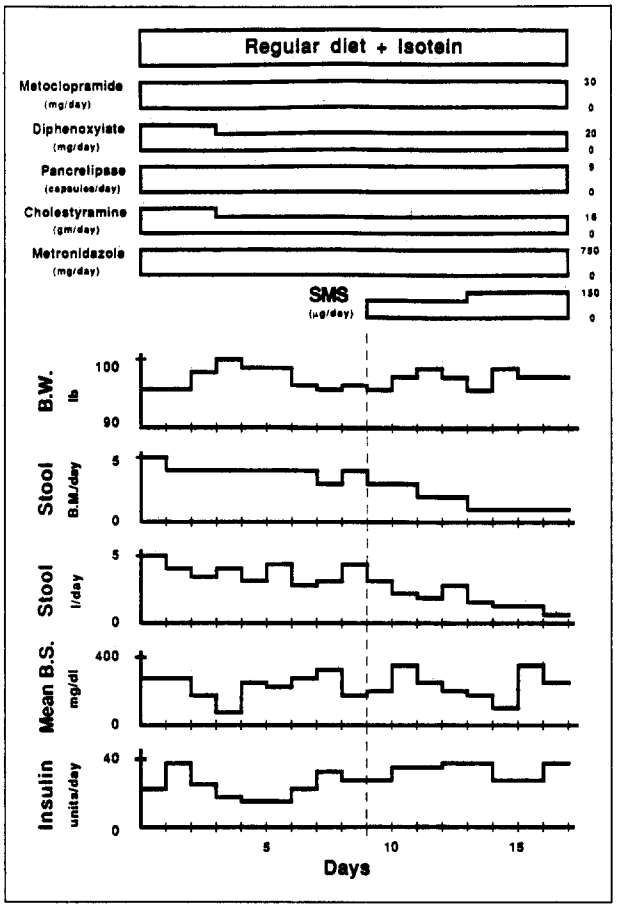


***Figure 10.*** *Clinical course of a diabetic patient with diarrhea that had persisted for 10 months and the response to differential treatment modalities. Vertical dashed line indicates the start of SMS 201-995 treatment. BW = body weight; BM = bowel movement; BS = blood sugar.*

## COMMENTS

Our objective in these studies was to determine if SMS 201-995 could control hormone-amine action at target tissues and limit excessive hormone production by the tumors of the gastroenteropancreatic axis, and to evaluate the analogue's effectiveness in regulating exocrine secretions by the gastrointestinal tract and the growth and differentiation of a number and variety of these tumors.

The gastrinoma syndrome is heterogeneous, comprising at least four clinical entities: (1) G-cell hyperfunction/hyperplasia, (2) benign sporadic gastrinoma, (3) gastrinoma with multiple endocrine neoplasia type I, and (4) metastatic gastrinoma [50,51]. Today, no single therapeutic intervention is universally applicable to this heterogeneous syndrome [1–3]. The use of native somatostatin-14 or somatostatin-28 to treat gastrinoma syndrome would require constant intravenous infusion [52]. A single injection of 100 $\mu$g of the long-acting somatostatin analogue inhibited pentagastin-stimulated gastric acid secretion in six healthy subjects [53]. Furthermore, in three patients with gastrinomas, 50 $\mu$g of SMS 201-995 produced an inhibition of gastric acid secretion and a parallel decline in serum gastrin levels [54]. Two fresh tumors from these patients were studied in vitro in a cell dispersion preparation, and SMS 201-995 reduced calcium-stimulated gastrin release by 50 percent in a dose-dependent manner [54]. Data on tumor progression have not been reported.

In our three patients with benign gastrinoma in whom acid secretion was not controlled by $H_2$-blockers, SMS 201-995 in doses of 50 to 100 $\mu$g every six to 12 hours suppressed gastric secretion and acid output by 85 and 95 percent, respectively. The rapid and complete inhibition of gastric acid secretion led to a striking clinical improvement and made surgery possible without other preoperative treatment. Nasogastric suction resulted in severe hypochloremic alkalosis; a single 50-$\mu$g injection of SMS 201-995 controlled acid secretion for the duration of the procedure. Acid secretion must be suppressed before nasogastric suction is begun. No anesthetic problems were encountered, hypotension did not occur, and the blood glucose level remained stable throughout the procedure. In Patient 2, after complete excision of the tumor, acid secretion did not immediately return to normal despite an appreciable lowering of serum gastrin. The dose of the analogue had to be increased to 800 $\mu$g per day and continued through the 7th postoperative day before gastric acid output was controlled. The patient did recover and remains free of ulcer symptoms or diarrhea. Why the patient's condition became refractory to SMS 201-995 during the postoperative period is difficult to explain. While large quantities of tumor gastrin could have been released during surgery, and exceeded the inhibitory capacity of the lower doses of SMS 201-995, the longest half-life of known gastrin peptides is about 40 minutes, which would make this an unlikely cause for the persistently high gastric acid secretion. Gastrin precursors with a half-life considerably in excess of that of G34 or G17 may have been released, but we have no data to confirm or refute this. An alternate explanation is that the tumor contained an inhibitor of acid secretion, such as somatostatin-14 or -28, which was simultaneously removed with the source of gastrin, thus unleashing acid secretion. However, the measured levels of circulating somatostatin did not support this.

These patients were treated with SMS 201-995 and surgery may now be a valid option. However, the long-term safety of the drug, especially in patients with gastrinoma syndrome who probably require life-long antisecretory agent(s), remains to be established.

In patients with surgically inaccessible or metastatic tumors, the situation is quite different. At least 60 percent of gastrinomas are malignant and, at operation, more than 50 percent have already metastasized to the liver [1–3]; the tumor, therefore, is the major threat to survival for patients with malignant gastrinoma since gastric acid hypersecretion is associated with reduced morbidity and mortality [3,7].

Various drugs and specific chemotherapeutic agents such as streptozotocin [55,56], 5-fluorouracil [56,57], doxorubicin [2], tubercidin [58], or radiation [59] have been used to manage unresectable or metastatic gastrinomas. These therapeutic modalities may provide palliative relief for some patients, but the overall results have been disappointing. Both experimental [60] and clinical findings [18,19] suggest that SMS 201-995 may be useful hormonal therapy for some malignant gastroenteropancreatic endocrine tumors. In two vipoma cases, the analogue not only controlled the diarrhea, but also induced a shrinkage of liver metastases after five and 14 months of treatment [18,19]. In contrast, two patients with metastatic gastrinoma unresponsive to chemotherapy did not show a response to SMS 201-995; neither tumor growth nor the serum gastrin levels were controlled. However, one gastrinoma patient (Patient 4) who showed a response to 15 courses of chemotherapy and remained well for five years, also had a response to SMS 201-995. In fact, after three months of treatment with the analogue, one tumor shrank but another continued to grow. Although the patient's amino-terminal/carboxy-terminal gastrin ($NH_2$:COOH) ratio was abnormally high when his disease was active, it dropped when he was in remission. This suggests that metastases may process gastrin differently; the "small (regressing) tumor" contained predominantly G-34, while the "big (growing) tumor" contained predominantly G-17. Whether this reflects a transcriptional event, mutation in the gastrin gene, or post-transcriptional processing clearly needs to be studied. Our data indicate that

metastatic tumors with a high $NH_2$:COOH ratio are unlikely to respond to the somatostatin analogue.

The mechanism of action of SMS 201-995 may not be a direct effect, but rather may be mediated indirectly. Incubation of the metastatic tumor with the analogue stimulated the release of gastrin, in contrast to the observed inhibition of gastrin release in benign gastrinoma [54]. This may reflect loss of somatostatin receptors in the metastatic tumors, removal of the mediator of inhibition of cell growth when the tumor is resected, or an effect of the drug on tumor growth either by altering local growth promoters or reducing tumor blood flow. A reduction in blood flow to the tumor induced by SMS 201-995 in patient 3 was demonstrated through angiography; however, further studies are required to establish this conclusively.

Both insulin and glucagon are inhibited by infusions of somatostatin-14. In the fasting state, the inhibition of these two hormones coexists with a decrease in the blood glucose concentration [61–63]. This phenomenon is thought to be mediated by the dominant inhibition of glucagon [64–66]. Furthermore, in patients with insulinomas, hypoglycemia might be expected since hypoglycemia has been seen to increase with SMS 201-995 during insulin infusion [64,67]. However, selective inhibition of insulin with various analogues of somatostatin appears to offer the most promise for treating insulinomas. Mandarino et al [64] demonstrated in vitro selective pharmacologic effects of somatostatin-14 on glucagon, insulin, and growth hormone secretion.

The effects of SMS 201-995 on insulin secretion in humans is being studied; preliminary data suggest that subcutaneous injections of the analogue may inhibit insulin secretion more than glucagon does in normal subjects. This may explain the findings in two of our patients that treatment with SMS 201-995 ameliorated their hypoglycemia. In these patients, insulin was inhibited to 75 percent of basal levels, but glucagon was inhibited to only 30 percent of basal levels, and the inhibition was transient with recovery to near basal levels by 48 hours. With SMS 201-995, parallel inhibition of C-peptide levels occurred, and the ratio of insulin to proinsulin was not altered. This indicates that the effects of the analogue were achieved through the inhibition of insulin secretion and not through a change in the biologically active product; therefore, SMS 201-995 at these doses may effectively inhibit insulin release in certain patients [68–70]. However, larger doses of SMS 201-995 given more frequently may be necessary to control peptide secretion in glucagonoma patients [71]. The two patients with benign insulinomas illustrate some of the interesting pharmacologic effects of the analogue. Clearly hyperinsulinism and consequent hypoglycemia were responsive to the inhibitory effects of SMS 201-995, which is indicative of a preferential effect of SMS 201-995 on inhibition of insulin as compared with glucagon secretion. The insulin inhibitory effect of the analogue enabled patients to tolerate longer periods of fasting and maintained their euglycemia throughout a complicated operative procedure.

A similar beneficial effect was observed in a newborn with nesidioblastosis. However, we did not have the opportunity to study the infant prior to 95 percent pancreatectomy, and the effects of SMS 201-995 did not appear for several days; however, the use of this drug in nesidioblastosis merits further study. The infusion of somatostatin-14 is also capable of inhibiting insulin secretion in this syndrome [68].

In contrast to these three patients, we found that SMS 201-995 did not prolong the hypoglycemia-free interval in two patients with pancreatic tumors. In both cases, the drug inhibited the secretion of glucagon and appeared to delay the absorption of nutrients from the gastrointestinal tract. The period of fasting was not extended, and blood glucose levels did not rise with meals so the frequency and intensity of hypoglycemic events were not reduced. A case of metastatic insulinoma [69] has been reported in which control of the patient's hypoglycemia could have been due to either SMS 201-995 therapy or the fact that the tumor appeared to secrete predominantly proinsulin, which is less effective than insulin in lowering blood glucose concentration.

Patients with organic hyperinsulinism may show improvement if insulin secretion is predominantly suppressed; however, their condition may deteriorate under any of the following conditions: dominant suppression of glucagon secretion; inhibition of hepatic glucose production; delay in the absorption of nutrients from the gastrointestinal tract; or enhancement of the action of insulin. The effects of SMS 201-995 in each of these states should be studied while the blood glucose concentration is carefully monitored: In patients with benign single adenomas, surgical resection of the tumor will remain the treatment of choice; however, our cases demonstrate the potential of SMS 201-995 in managing hyperinsulinism. Patients with multiple adenomas, nesidioblastosis, or malignant insulinomas may benefit from SMS 201-995 in combination with more traditional forms of therapy.

Although recent reports suggest that somatostatin and its analogues are potent inhibitors of flushing caused by carcinoid tumors [43,44], their therapeutic usefulness is limited by their multiple effects on many secretory cells and their short duration of action [72,73]. SMS 201-995 has been used to treat endocrine tumors [8,39,40] associated with flushing and diarrhea.

Most carcinoid tumors arise from enterochromaffin cells of the gut, which contain granules of serotonin, substance P, and motilin, and are heterogeneous, multipotential lesions that may secrete many humoral agents. Calcitonin, motilin, vasoactive intestinal peptide, ACTH, enter-

oglucagon, and substance P are found in carcinoid tumor tissue extracts and in the serum of some patients with carcinoid syndrome. Flushing, diarrhea, bronchospasm, and right-sided heart failure have been ascribed mainly to serotonin, prostaglandins, and the kinins. Surgical removal of carcinoid tumors is the treatment of choice; when they are metastatic, chemotherapy is used. In addition to the antineoplastic drugs, several pharmacologic agents have been used to block the effects of these peptides. Parachlorophenylalanine, alpha-methyldopa [74,75], cyproheptadine, methotrimeprazine, and methysergide maleate are specific to serotonin and are used to control flushing, diarrhea, and bronchospasm. Corticosteroids block kallikrein release but are rarely effective. Aprotinin, a kallikrein trypsin inhibitor, and epsilonamino caproic acid have been used to manage refractory hypotension and bronchospasm in carcinoid crisis. Phenoxybenzamine and antihistamines are used occasionally [34–38,74,76–78].

Somatostatin has been shown to inhibit diarrhea and bronchospasm in patients with carcinoid syndrome and to inhibit pentagastrin-induced flushing [43,79]. Davis et al [80] investigated the effect of somatostatin infusion on jejunal water and electrolyte transplant in a patient with secretory diarrhea due to malignant carcinoid syndrome. Net secretion was inhibited, and absorption was stimulated. In our nine patients with the carcinoid syndrome, flushing and diarrhea were readily controlled with low doses of SMS 201-995. In contrast, we found no effect on circulating serotonin levels and in one patient a rise in a biologically inert ACTH to 100 times that of normal occurred, without the development of Cushing's syndrome. Tumors did not grow during the three to six months of treatment, and in two patients the tumors actually seemed to shrink.

In studies of perfused small intestine of three patients, SMS 201-995 induced net water and electrolyte absorption in two; therefore, it was not surprising that all our patients with secretory diarrhea showed improvement during therapy with SMS 201-995 [81,82]. However, when steatorrhea occurred, pancreatic supplements were needed.

Our experience with SMS 201-995 therapy in a patient with diabetic diarrhea unresponsive to conventional drug treatment was most interesting. Somatostatin was considered because it affects both epithelial transport and intestinal motility [79]. Native somatostatin as well as the analogue are known to effectively reduce stool output in diarrhea syndrome associated with endocrine tumors [80,83–85] and other conditions [86–89]. SMS 201-995 retains the critical portion of the molecule Phe-Trp-Lys-Thr[13] for gut-specificity [88], and reportedly changed net water movement to absorption in a patient with severe secretory diarrhea due to pancreatic cholera syndrome [89]. In contrast to vipoma patients [83,84,89], the patient with diabetic diarrhea did not over-secrete water or electrolytes; nevertheless, subcutaneous injection of the drug did enhance the net absorption of water and electrolytes at the peak (30 minutes) SMS 201-995 concentration [89].

The possibility that fasting hypoglycemia and postprandial hyperglycemia will develop in diabetic patients receiving long-term therapy with SMS 201-995 is of concern [90]. A single SMS 201-995 subcutaneous injection in 10 patients with insulin-dependent diabetes mellitus reduced the insulin dose without causing postprandial hyperglycemia or hypoglycemia [90]. In our diabetic patient, the insulin dose required to maintain relative normoglycemia was constant over four months of treatment with the analogue, but her food intake and cessation of diarrhea may have necessitated an increase in insulin. Long-term SMS 201-995 treatment of brittle diabetic patients with autonomic neuropathy of the gut may stabilize the diabetic control by suppression of counterregulatory hormones and enhancement of the absorption of nutrients from the intestine.

In the patient with incapacitating diarrhea refractory to all medications, SMS 201-995 reduced the volume and frequency of stools, and enabled the patient to return to a fairly normal life-style. Thus, for some patients with "diabetic diarrhea" unresponsive to available therapy, the analogue may be useful adjunctive treatment.

In summary, in these studies we have demonstrated a variety of responses to SMS 201-995.

- In three patients with benign gastrinomas, the drug decreased acid and gastrin secretion that had been uncontrollable with $H_2$-receptor blocking drugs.
- In two patients with metastatic gastrinoma, the tumors continued to grow and gastrin levels could not be reduced despite very large doses of the analogue.
- Three patients with benign insulinoma maintained euglycemia with SMS 201-995 therapy, as did a neonate with nesidioblastosis. Two elderly patients did not experience prolongation of their hypoglycemia-free interval.
- The response in carcinoid syndrome was variable. Flushing and diarrhea were readily controlled, sometimes necessitating the use of pancreatic supplements. Tumor growth appeared to be relatively refractory to the drug, but in selected instances there appeared to be some degree of regression or arrest of further growth. There was, however, no correlation between hormone or amine output and the clinical response or the growth of the tumor.
- The analogue controlled diarrhea and decreased vasoactive intestinal peptide levels in two patients with vipoma syndrome. The tumor infarcted in one patient, an effect that may be related to the vascular effects of the drug. Diabetic diarrhea could be controlled with SMS 201-995 without changing diabetic control when all other forms of intervention had failed.

Our investigations have led us to the following conclusions:

- SMS 201-995 controls gastroenteropancreatic tumor symptomatology in most patients.

• Hormonal responses to the somatostatin analogue do not always parallel clinical responses.

• The analogue's effect on gastroenteropancreatic tumor growth and secretion is variable.

• SMS 201-995 controls diarrhea due to carcinoid tumors, vipomas, and diabetes.

• Diarrhea may develop in some patients during treatment with the analogue and pancreatic enzyme replacement may be required.

• Occasionally, a patient may have a local skin reaction to SMS 201-995, but the drug will not have to be withdrawn.

• SMS 201-995 may result in tumor infarction through an effect on blood flow to the tumor.

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## Discussion

**Dr. G.W. Geelhoed:** What are your thoughts on the use of SMS 201-995 as antineoplastic therapy, particularly in view of its relative non-toxicity? Further, can it be used as a substitute for conventional, first-line antineoplastic therapy?

**Dr. Aaron I. Vinik:** I don't think we know the answer. I think SMS 201-995 is an important therapeutic agent for certain tumor situations. The decision to use the drug is easy when the patient has not shown a response to cytotoxic therapy. Although the neuroendocrine tumors are largely indolent, patients with hepatic metastases have an increased mortality. Therefore, in my opinion, those who fail to show a response to chemotherapy should be given a trial with SMS 201-995.

**Dr. Geelhoed:** If I may expand on this, would you recommend using SMS 201-995 in combination with conventional treatment in patients in whom symptoms are controlled, e.g., with $H_2$ antagonists in gastrinoma patients?

**Dr. Vinik:** I recommend using SMS 201-995 when chemotherapy fails and progression of the tumor is demonstrated. I cannot, however, recommend it as primary therapy until its safety, efficacy, and toxicity have been better elucidated. The combination of SMS 201-995 and conventional chemotherapy is certainly intriguing, but it is much too early to predict what could occur.

**Dr. Attila Ertan:** Would you recommend either low-dose or high-dose SMS 201-995 therapy in patients with apudoma to prevent hypoglycemia? Further, in our experience, there seems to be a discrepancy between the preferential effects on serum insulin versus glucagon inhibition of natural somatostatin versus SMS 201-995. Please comment.

**Dr. Vinik:** It would be ideal to have a selective somatostatin analogue that would suppress insulin but not glucagon. And in fact, in normal subjects, low doses of SMS 201-995 may not induce hypoglycemia because of selective insulin inhibition. However, in patients with tumors, hypoglycemia may be observed with SMS 201-995 because of greater sensitivity to glucagon inhibition. Furthermore, the dose required in tumor patients is much higher. I cannot say from our limited experience whether or not the observed hypoglycemia will be a function of the benign adenomas, multiple adenomas, nesidioblastosis, the malignant tumor, or even age.

**Dr. William Y. Chey:** Would you elaborate on the use of SMS 201-995 in the asymptomatic patient in whom there is documented tumor progression?

**Dr. Vinik:** At the University of Michigan, all patients with metastases receive cytotoxic therapy. If the tumor continues to grow, we administer SMS 201-995. At this time, we do not consider SMS 201-995 to be a first-line chemotherapeutic agent.

**Dr. William B. Malarkey:** Could you comment on the use of lithium in patients with the watery diarrhea syndrome?

**Dr. Vinik:** Based on prior observations that lithium is an antidiarrheal agent, we tried it and it worked. However, we elected to stop lithium because of its toxicity and to use only SMS 201-995, which has minimal toxicity. Although combining the two agents could potentiate their effects, this has not been established clinically.

**Dr. Manuel Tzagournis:** Have vasoactive intestinal peptide and other gut hormones been measured in diarrheal states besides the water diarrhea syndrome, e.g., diabetic diarrhea? Has somatostatin been tried in other diarrheal states?

**Dr. Vinik:** Dr. O'Dorisio can you answer that?

**Dr. Thomas M. O'Dorisio:** No, except for true vipomas

and their associated watery diarrhea syndrome, and perhaps non-tropical sprue wherein vasoactive intestinal peptide is sometimes elevated, other casual peptide mediators have not been described. Some secretory diarrheas are not vasoactive intestinal peptide-mediated. SMS 201-995 has been used in other states of secretory diarrhea; I know that in three of six cases in the United States, SMS 201-995 alleviated the diarrhea. One of these patients (not one of Dr. Vinik's) had diabetic diarrhea.

**Dr. William H. Daughaday:** Did SMS 201-995 affect the growth of the child with nesidioblastosis?

**Dr. Vinik:** He is growing well, but some steatorrhea developed that required pancreatic supplementation. Hopefully, his condition will improve as he grows, as is often the case.

**Dr. M. Sue O'Dorisio:** I would like to offer a possible interpretation to the varied responses of the tumors to SMS 201-995. Subsets of metastatic receptors may occur naturally for which the analogue may in some cases act as an agonist, and in other cases as an antagonist. In addition to neuroendocrine tumors, there may be a spectrum of tumors, including some having no somatostatin receptors, others having any of the receptor subclasses, and still others having none. This may explain the observed differences in response to the analogue.

**Dr. Vinik:** I concur with Dr. Sue O'Dorisio and would extend this line of thinking. Not only may the tumor have or require a SMS 201-995 receptor, but also the endothelial or smooth muscle cells of the tumor blood vessels may have a different tissue receptor.

**Dr. Dorothy Becker:** No one has mentioned the effects of long-term SMS 201-995 therapy on growth hormone or other non-pancreatic hormones. We know that SMS 201-995 inhibits growth hormone in acromegaly, but what happens long-term when children require long-term treatment with the analogue, such as your case of nesidioblastosis?

**Dr. Vinik:** Your question demands an answer; however, we have not had the opportunity to follow these patients long-term.