Digestive Diseases and Sciences, Vol. 38, No. 2 (February 1993), pp. 309–315

Effect of Chronic Octreotide Treatment on Intestinal Absorption in Patients with Acromegaly

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The adverse gastrointestinal effects of octreotide, a synthetic analog of somatostatin, have not been fully elucidated. Low-dose octreotide frequently causes adverse gastrointestinal symptoms in normal individuals. We investigated the adverse gastrointestinal effects of high-dose octreotide, which is required for the normalization of growth hormone hypersecretion in some patients with acromegaly. Patients with acromegaly (N = 8) were treated with octreotide, 450 μg/day, then 1500 μg/day for two months at each dosage. Carbohydrate absorption was assessed using the D-xylose test, and fat absorption using fecal fat excretion and serum carotene concentrations, at baseline, at each dosage of octreotide, and after one month of washout. Ultrasonography was used to monitor for cholelithiasis. Growth hormone and insulin-like growth factor-I concentrations were significantly suppressed at both dosages. Adverse gastrointestinal symptoms were mild and transient. D-Xylose absorption remained normal at each dosage and after one month of washout. Fecal fat excretion increased from 7 ± 2 to 12 ± 2 g/24 hr (P < 0.05) after the higher dosage and resumed baseline levels after the washout. Mean fasting serum carotene levels remained normal, and carotene loading test (15,000 units three times a day for three days) was unreliable in identifying patients with high fecal fat. No new cholelithiasis was detected by ultrasonography. One of two patients with preexisting cholelithiasis developed biliary colic several days after the treatment period. Although steatorrhea was common, small intestinal absorptive capacity was otherwise unchanged by four months of high-dose octreotide treatment, which significantly suppressed growth hormone secretion in acromegalic patients.

KEY WORDS: intestinal absorption; octreotide; acromegaly; xylose; fat; carotene; cholelithiasis; adverse effects.

Octreotide (SMS 201-995, Sandostatin, Sandoz, East Hanover, New Jersey) is a synthetic octapeptide analog of the native hormone somatostatin, which is widely distributed in the body and has effects upon various systems (1, 2). Octreotide has been shown to reduce growth hormone (GH) hypersecretion in patients with acromegaly (3), as well as the symptoms of malignant carcinoid syndrome and VIPoma (4). To date it has been approved by the Food and Drug Administration for use for the latter two indications, while its use for other conditions is still under investigation. In particular, certain po-

Manuscript received February 25, 1992; revised manuscript received July 10, 1992; accepted July 17, 1992.

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This work was supported by Sandoz Pharmaceuticals Corp., East Hanover, New Jersey.

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0163-2116/93/0200-0309$07.00/0

tential adverse effects of the drug have yet to be defined.

Previous studies have shown that administration of octreotide produces a variety of adverse gastrointestinal effects (4, 5), which mimic those found in patients with somatostatinomas, such as diarrhea, steatorrhea, and formation of biliary stones (6). The aim of this study was to investigate whether chronic treatment with high doses of octreotide over four months caused malabsorption in patients with acromegaly, as measured by D-xylose absorption, fecal fat excretion, and serum carotene concentrations.

MATERIALS AND METHODS

Patients. The study group consisted of eight patients (five males, three females, 23–60 years of age) with active acromegaly. Earlier safety studies have shown that adverse gastrointestinal symptoms occur commonly in normal individuals at relatively low doses of octreotide. In contrast, patients with acromegaly require chronic therapy and sometimes at high doses (600–1500 μg/day) in order to suppress their growth hormone and insulin-like growth factor-I (IGF-I) concentrations. Thus, this group of patients was chosen because they would require higher doses of octreotide and would benefit from this protocol by normalization of GH secretion. All patients had been treated for acromegaly previously: transsphenoidal or transfrontal craniotomy in all, radiotherapy in six patients, and bromocriptine for up to 11 years in six patients. Bromocriptine was ceased 2–12 months prior to this study. All patients had also been treated with octreotide, and it had been stopped one month to three years prior to this study. Five patients were included in a previous report on the effect of octreotide on GH secretion in acromegaly (3). The diagnosis of active acromegaly was reconfirmed before commencement of this study clinically and by high plasma GH and IGF-I concentrations. Three patients (#5, 7, and 8) had intact pituitary function and the other five patients had hypopituitarism, which was treated with appropriate replacement therapy.

Patients 5 and 6 had non-insulin-dependent diabetes controlled with diet and oral hypoglycemic agents. Patient 8 had previously been treated for Graves disease and had been euthyroid without thyroxine supplement for several years. None had any significant hepatic disease. Patients 3 and 7 had asymptomatic cholelithiasis. Patient 5 had morbid obesity and had undergone reduction gastroplasty and prophylactic cholecystectomy seven years previously. All had a history of normal and formed bowel movements (once every one or two days), and none were taking medications known to affect gastrointestinal function.

Protocol. The protocol was approved by the local Institutional Review Board and written informed consent was obtained from every patient. Octreotide was self-administered subcutaneously by the patients. Studies were performed four times: at baseline, after octreotide was administered at 150 μg three times a day for nine weeks, after the dose was escalated to 250 μg three times a day for two weeks followed by 500 μg three times a day for six weeks, and finally after a five-week washout period.

At every visit, a detailed clinical history was taken, with specific emphasis on the gastrointestinal system. Patients were asked whether their bowel movements increased in frequency but had unchanged consistency, had unchanged frequency but became soft or loose, or there was a combination of both soft or loose stools together with the increased frequency of bowel movements (diarrhea). Standard biochemical and hematologic analyses, thyroid function tests, glycosylated hemoglobin, plasma IGF-I, and serum GH concentrations were measured after an overnight fast. Blood was drawn for GH hourly for 5 hr (0800–1300 hr) at baseline and at the postwashout visit. At the two visits when patients were taking octreotide, the first blood sample was drawn immediately before the drug was administered at 0800 hr, and then hourly samples were drawn from 1000 to 1400 hr.

At every visit, the D-xylose testing was performed. Patients ingested 25 g D-xylose (Adria, Columbus, Ohio) in 500 ml water immediately after emptying the bladder in the morning after an overnight fast. Plasma xylose concentration was measured immediately before, and at 30, 60, and 120 min after ingestion of D-xylose. Urine was collected over 5 hr following the ingestion for measurement of urinary xylose excretion and calculation of creatinine clearance. During the test, patients were allowed to ingest water *ad libitum* only. At the two visits when patients were taking octreotide, D-xylose was ingested 1 hr after the injection of octreotide.

Fecal fat excretion was measured using a 72-hr fecal collection prior to each visit. Patients consumed 100 g fat per day for three days prior to and during the collection period. Fasting serum carotene concentration was measured at each visit. At the end of the high-dose treatment period (with octreotide 500 μg three times a day), fasting serum carotene concentration was also measured after three days of β-carotene (Freeda Vitamins, New York, New York) 15,000 units three times a day with meals while maintaining 100 g per day fat consumption. Compliance with fat consumption was confirmed by the patients' written food records. Upper abdominal ultrasound examination was performed at baseline and during low- and high-dose octreotide treatment to monitor for gallstones and was repeated after the washout period in any patient who had gallstones detected earlier.

IGF-I was assayed by Smith-Kline Laboratories (Van Nuys, California) using the method of Furlanetto et al (7). Fecal fat was assayed by Mayo Clinic Laboratories (Rochester, Minnesota) using a gravimetric method (8, 9). All other biochemical measurements were done by Metpath Laboratories (Teterboro, New Jersey). GH was assayed by double antibody RIA (10). Plasma and urinary xylose were assayed spectrophotometrically (11). Serum carotene was assayed by spectrophotometrically (12).

Data were analyzed by analysis of variance with repeated measures. Data are shown as mean ± SE. Statistical significance was assessed at $P < 0.05$.

RESULTS

Serum GH and Plasma IGF-I Concentrations. Mean GH concentrations were elevated at 12.8 ± 3.4 μg/liter (normal < 4.5 μg/liter) at baseline. Mean GH for the whole group decreased significantly to 4.0 ± 0.7 μg/liter at nine weeks of treatment with octreotide 150 μg three times a day, but did not fall further after another eight weeks of treatment at 500 μg three times a day (3.7 ± 0.8 μg/liter). Five weeks after cessation of the drug, mean GH concentrations rose significantly to 13.1 ± 4.5 μg/liter, which was similar to the baseline value. Plasma IGF-I concentrations (normal ≤ 318 μg/liter in men, ≤ 270 μg/liter in women) showed the same pattern of changes (baseline: 882 ± 95; 150 μg three times a day dose: 472 ± 59; 500 μg three times a day dose: 389 ± 65; and five weeks postwashout: 861 ± 78 μg/liter.

Adverse Symptoms. All patients experienced gastrointestinal side effects during treatment with octreotide, namely abdominal gas (seven patients), transient nausea postinjection (three patients), soft stools of unchanged frequency (three patients), increased frequency of bowel movements (one patient from one bowel movement every other day to one to two formed stools every day) and diarrhea (two patients, five to seven bouts per day). In most cases, the symptoms were present transiently (up to two days) at the start of the study, or when the dose of octreotide was escalated, while in others the symptoms decreased but lasted for the entire treatment period. One patient took 200 μg three times a day instead of 150 μg three times a day at the beginning of the study. He experienced severe abdominal gas and diarrhea, which persisted until the dosage was decreased to the originally prescribed 150 μg three times a day several days later. When the dosage was increased to 500 μg three times a day, he experienced the same symptoms, which subsided when the dose was reduced to 450 μg three times a day, which was the final dosage in this patient. In the other seven patients no side effects were severe enough to require a decrease in the dose of octreotide at any time, and the highest dose taken was 500 μg three times a day. All symptoms disappeared within one to two days of stopping the drug on completion of the treatment protocol by all patients. Fecal weight (72 hr collection) at baseline was 338 ± 82 g; after octreotide 150 μg three times a day it was 451 ± 92 g; after 500 μg three times a day, 472 ± 109 g; and after one month of washout, 305 ± 58 g. No difference between the time points was detected using ANOVA with repeated measures.

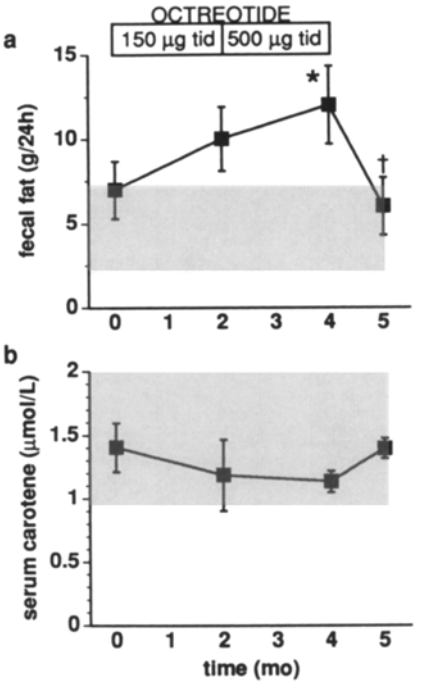

Fig 1. Assessment of fat absorption in eight patients with acromegaly before and after treatment with octreotide at 150 μg three times a day and 500 μg three times a day for two months at each dose, and after a one-month washout. Normal ranges are shown by the shaded areas. *$P < 0.05$ vs baseline. †$P < 0.05$ vs 500 μg three times a day.

Fecal Fat Excretion and Serum Carotene Concentrations. At baseline, fecal fat excretion (Figure 1a) was elevated in patients 1 and 2 (9 and 16 g/24 hr, normal 2–7 g/24 hr). Both patients had not been taking octreotide for 0.7 years prior to this study. The mean for the entire group was at the upper limit of normal range (6.6 ± 1.7 g/24 hr). When octreotide was administered at 150 μg three times a day, an additional three patients had elevated fecal fat excretion, and the mean fecal fat excretion rose to 9 ± 2 g/24 hr, although this was not statistically significant. When octreotide was taken at high dose (500 μg three times a day) a total of six patients had elevated fecal fat excretion, and the mean fecal fat excretion (11 ± 2 g/24 hr) for the entire group was significantly higher ($P < 0.05$) than the baseline value. After the five-week washout, only patients 1 and 6 had elevated fecal fat excretion (10 and 16 g/24 hr) and the mean value for the whole group (6 ± 2 g/24 hr) was similar to the baseline.

Fasting serum carotene concentration (Figure 1b) at baseline was mildly decreased in two patients

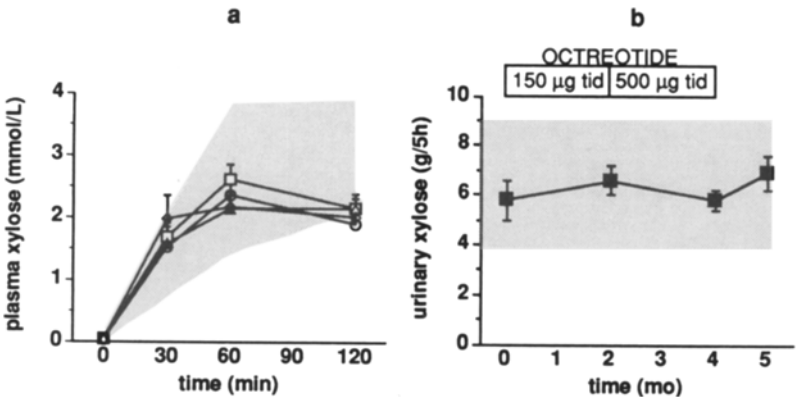

Fig 2. Plasma D-xylose concentration (a) and urinary D-xylose excretion (b) in eight patients with acromegaly during D-xylose test performed before and after treatment with octreotide 150 μg three times a day and 500 μg three times a day for two months at each dose, and after a one-month washout. Normal ranges are shown by the shaded areas. (a) □, baseline; ○, after two months of octreotide 150 μg three times a day; △, after another two months of octreotide 500 μg three times a day; ◇, after one month of washout.

(0.80 and 0.85 μmol/liter, normal 0.93–4.70 μmol/liter) and normal in the other six patients. When octreotide was taken at a low dose (150 μg three times a day), four of the eight patients had mildly decreased fasting serum carotene concentrations (0.82–0.89 μmol/liter), but at a high dose (500 μg three times a day) only two had decreased values (0.85 μmol/liter in both). After washout, serum carotene concentration was normal in every patient. Mean serum carotene concentration for the entire group was statistically unchanged with octreotide treatment (1.40 ± 0.19 at baseline, 1.18 ± 0.28 and 1.13 ± 0.08 μmol/liter at octreotide 150 μg three times a day and 500 μg three times a day, respectively) as well as after the five-week washout (1.40 ± 0.08 μmol/liter). Three patients exhibited a subnormal rise of serum carotene (0.22–0.32 μmol/liter, normal ≥ 0.65 μmol/liter) postcarotene loading at the end of the high-dose treatment period, but only two of them had increased fecal fat (9 and 18 g/24 hr).

D-Xylose Absorption. Plasma D-xylose concentrations during the D-xylose test were within the normal range throughout the study (Figure 2a). Urinary xylose excretion over 5 hr after xylose ingestion (Figure 2b) was normal at baseline (5.8 ± 0.8 g) and unchanged with octreotide treatment (6.6 ± 0.6 and 5.8 ± 0.4 g at octreotide 150 μg three times a day and 500 μg three times a day, respectively), as well as after the five-week washout (6.9 ± 0.7 g). At no instance did urinary D-xylose excretion decline to a subnormal range. Creatinine clearance was normal at baseline (2.22 ± 0.23 ml/sec) and unchanged with octreotide treatment (2.08 ± 0.20 and 2.08 ± 0.23 ml/sec, with octreotide 150 μg three times a day and 500 μg three times a day, respectively), as well as after the five-week washout (2.12 ± 0.23 ml/sec).

Cholelithiasis. Serial upper abdominal ultrasound examination showed no changes from baseline in patients 3 and 7, who had cholelithiasis at baseline, or in the other five patients who remained without gallstones during the treatment period. Patient 3 had a bout of biliary colic five days after octreotide had been ceased and underwent elective cholecystectomy 10 days later.

Serum Biochemistry. Mild to moderate hyperphosphatemia was present in six patients at baseline (1.39–1.71, normal 0.71–1.36 mmol/liter), in two (1.45 and 1.58 mmol/liter) when treated with octreotide 150 μg three times a day, in three (1.39–1.45 mmol/liter) with 500 μg three times a day, and in five (1.45–1.58 mmol/liter) after washout. Serum inorganic phosphate concentration for the entire group decreased from 1.42 ± 0.06 mmol/liter at baseline to 1.26 ± 0.06 mmol/liter ($P < 0.05$) when octreotide was taken at 150 μg three times a day and remained at the same level during the higher dosage of octreotide. After the washout it increased ($P < 0.05$) to the baseline value (1.46 ± 0.06 mmol/liter). Serum calcium, protein, albumin, alkaline phosphatase, alanine amino transferase, and aspartate amino transferase concentrations were normal and stable throughout the protocol. In patient 6, who had non-insulin-dependent diabetes mellitus, both

fasting serum glucose concentrations (baseline: 14.2 mmol/liter, 150 μg three times a day dose: 6.6 mmol/liter, 450 μg three times a day dose: 8.3 mmol/liter) and glycosylated hemoglobin (baseline: 9.5%, 150 μg three times a day dose: 8.7%, 450 μg three times a day dose: 6.2%) decreased with octreotide treatment and rose towards baseline levels after the washout (15.3 mmol/liter and 7.7%, respectively). In patient 5, glycosylated hemoglobin improved slightly with high-dose (500 μg three times a day) but not with low-dose (150 μg three times a day) octreotide (baseline: 10.2%, 150 μg three times a day dose: 10.4%, 450 μg three times a day dose: 9.4%), and fasting serum glucose concentrations (baseline: 11.6 mmol/liter, 150 μg three times a day dose: 10.1 mmol/liter, 450 μg three times a day dose: 14.3 mmol/liter) were essentially unchanged or higher at the two different doses, respectively. After the washout, glycosylated hemoglobin was 10.4%, similar to baseline, and fasting serum glucose concentration was 14.5 mmol/liter in this patient. For the entire group, glycosylated hemoglobin and thyroid function tests (total and free thyroxine, and thyroid stimulating hormone) remained normal and unchanged throughout the study. Routine hematologic analyses were normal throughout the study.

DISCUSSION

The natural hormone and neurotransmitter somatostatin is widely distributed in the body, including the hypothalamus, nervous system, and gastrointestinal tract. Its inhibitory action affects endocrine, exocrine, as well as neurological functions (1, 2). The application of somatostatin to the treatment of disorders involving hyperfunction of its target organs has been limited by its lack of specificity and short half-life, and a rebound of the processes inhibited on cessation of somatostatin infusion. These problems have been largely overcome by the development of the somatostatin analog octreotide (13). Octreotide is approved by the Food and Drug Administration for treatment of the symptoms of malignant carcinoid syndrome and VIPoma. Its use in other diseases such as acromegaly, thyrotropin-producing pituitary tumors, and some nonmalignant diseases of the gut (4) is still experimental. Certain adverse effects have yet to be elucidated.

Previous studies have shown that, overall, octreotide is well tolerated and major side effects are rare. The more common side effects involve the gastrointestinal tract. Studies in normal individuals and patients have shown that mild transient abdominal bloating, gas, and cramping occur frequently during the initial days to weeks of treatment (4, 5), which is similar to the present study. The initial adverse symptoms decreased to easily tolerable levels with continuing octreotide therapy at the same dose in all but one of our patients. In that patient, symptoms appeared to be dose-dependent and did not abate until the dose was decreased, but even so, tolerance to the drug in terms of adverse symptoms was evident by their considerably milder and transient nature when the dose was increased further after several more weeks of treatment.

The biologic efficacy of octreotide and the adherence to therapy in this study were verified in each patient by significant declines in plasma GH and IGF-I levels and by improvement of hyperphosphatemia and diabetic control in some subjects.

An increase in fecal fat excretion in six of eight patients during administration of octreotide in this study is consistent with those of many past studies in both normal subjects and patients with acromegaly (3, 5, 17), and indicates obvious fat malabsorption. In the present study, serum carotene concentration remained normal or near normal, similar to an earlier study (18). The maintenance of normal serum calcium and alkaline phosphatase concentrations during octreotide treatment is consistent with normal vitamin D absorption, and with the normal 25-hydroxy vitamin D and alkaline phosphatase concentrations in the earlier study (18). In the present study, the increase in serum carotene concentration after loading was subnormal (increment $<$ 0.65 μmol/liter) in only three patients, and only two of them had steatorrhea (fecal fat $>$ 7 g/24 hr). Thus, in contrast to an earlier study (19), we found that measurement of serum carotene with or without prior loading was considerably less sensitive and specific than quantification of 72-hr fecal fat. The mechanism by which octreotide causes fat malabsorption in patients with acromegaly appears to be via a decreased secretion of and gallbladder sensitivity to cholecystokinin (20). Somatostatin infusion inhibits bile formation (21), and octreotide may also have a similar effect. Additionally, pancreatic exocrine function has been shown to be suppressed by octreotide (22, 23) with 24 hr production of amylase and lipase being suppressed by 63 and 27%, respectively. The combination of exocrine pancreatic insufficiency and decreased biliary

function is likely to account for the gastrointestinal symptoms that occur in patients treated with octreotide. In support of this is the efficacy of pancreatic enzyme therapy in alleviating most of the gastrointestinal side effects of octreotide during the initial weeks of therapy (3).

D-Xylose absorption occurs in the duodenum and jejunum by passive diffusion and therefore reflects the functional absorptive capacity of the proximal small intestine (16). Renal excretion accounts for half the total D-xylose elimination and is dependent on the glomerular filtration rate (24). The combination of plasma D-xylose concentration at 1 hr, with 5-hr urinary excretion of D-xylose after ingestion of a 25-g D-xylose load has been shown to be approximately 95% specific and sensitive in discriminating normal from subnormal proximal small intestinal absorption (24). Our results show that using this test, proximal small intestinal absorption in this group of patients was normal and stable during and after octreotide treatment. The normality and stability of creatinine clearance in our patients validates the use of urinary D-xylose excretion as a measure of D-xylose absorption and for serial comparison. Our results are similar to those obtained in normal subjects given an intravenous bolus and continuous infusion of octreotide in a previous study (25). In contrast, a study using patients with acromegaly showed that peak plasma xylose concentration after ingestion of D-xylose was unchanged by octreotide treatment, but the rise in plasma xylose concentration was slightly delayed (26). However, in that study, D-xylose was administered with a meal rather than in the fasting state as was done in the present study. Since meal ingestion could alter D-xylose absorption (24), it is conceivable that this might explain the difference between the two studies.

In the present study, shortly after four months of treatment at the maximal dose (1500 μg/day) of octreotide, one of two patients who had preexisting gallstones developed biliary colic necessitating cholecystectomy; the other remained asymptomatic, and no patient developed new cholelithiasis. Cholelithiasis is present in up to 50% of patients receiving octreotide, similar to the 65% prevalence rate in patients with somatostatinomas (27). Gallbladder contractility is impaired by somatostatin and was completely abolished by injection of 100 μg octreotide subcutaneously prior to a meal in a group of patients with acromegaly who were receiving chronic octreotide treatment (20). Thus development of cholestasis and cholelithiasis may be expected with octreotide treatment. Whether our patients' biliary colic was precipitated by the recent course of octreotide cannot be verified, but the question of treating patients with preexisting cholelithiasis with the drug needs to be addressed.

In summary, we have shown that in this group of eight patients with acromegaly, adverse gastrointestinal symptoms during high-dose octreotide therapy were common, but most were mild and transient. Our results also show that fat malabsorption was common as detected by 72-hr fecal fat measurement, although maintenance of normal or near-normal serum carotene concentrations and normal serum calcium and alkaline phosphatase concentrations on a normal diet suggest that absorption of fat-soluble nutrients was probably maintained at or near normal levels. Measurement of serum carotene concentration after carotene loading was not useful in identifying patients with fat malabsorption. D-Xylose absorption remained normal, suggesting that octreotide did not affect the functional absorptive capacity of the proximal small intestine.

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