Treatment of psoriasis with chronic subcutaneous administration of somatostatin analog 201-995 (Sandostatin)

II. Effect on pancreatic and thyroid hormone

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■ Nine patients with psoriasis vulgaris were treated for 12 weeks with somatostatin analog, octreotide acetate (SMS 201-995) 50 or 100 μg by subcutaneous injection every 12 hours. The purposes of the study were to determine: (1) levels of insulin, glucose, glucagon, pancreatic polypeptide (PP), and SMS 201-995 after a subcutaneous injection of SMS 201-995 and ingestion of a standardized meal; (2) nocturnal (0200 h) thyroid stimulating hormone (TSH) levels before, during, and after treatment; and (3) the pharmacokinetics of SMS 201-995. Insulin peaks at 30 minutes were blunted from 65.8 ± 11.0 μU/mL without treatment to 26.7 ± 8.6 μU/mL and 7.7 ± 2.0 μU/mL after the 50- and 100-μg doses, respectively. Glucagon levels remained constant during the meal and were not affected by the 50-μg dose. Mean glucose levels were significantly elevated during insulin suppression. PP was also rapidly suppressed by SMS 201-995 and remained so for 4 hours after the injection. Nocturnal TSH was blunted after 12 weeks of treatment ($P \leq .05$). T4 and T3 resin uptake showed no depression, and patients remained clinically euthyroid. The plasma peak of SMS 210-995 occurred 30 minutes postinjection and half-life was longer than 2 hours. After chronic administration of SMS 201-995, insulin was suppressed with resultant mild carbohydrate intolerance that persisted throughout the treatment course.

□ INDEX TERMS: PSORIASIS; SOMATOSTATIN; SOMATOTROPIN □ CLEVE CLIN J MED 1990; 57:77–81

SOMATOSTATIN (SRIF), a tetradecapeptide that inhibits secretion of growth hormone, was initially isolated from the hypothalamus.[1] It was subsequently discovered in D cells throughout the gastrointestinal tract and pancreas.[2] SRIF suppresses the secretion of thyroid stimulating hormone (TSH) from the pituitary as well as several hormones from the pancreas.[1,3] In addition, SRIF inhibits gastric acid and pepsin secretion, gut motility, nutrient absorption, and splanchnic blood flow.[4]

The many actions of SRIF stimulated research into therapeutic applications; however, SRIF's short half-life (3 minutes) made it clinically impractical. Furthermore, the rebound postinfusion hypersecretion of hormones in acromegalic patients made it clinically unattractive.[5,6]

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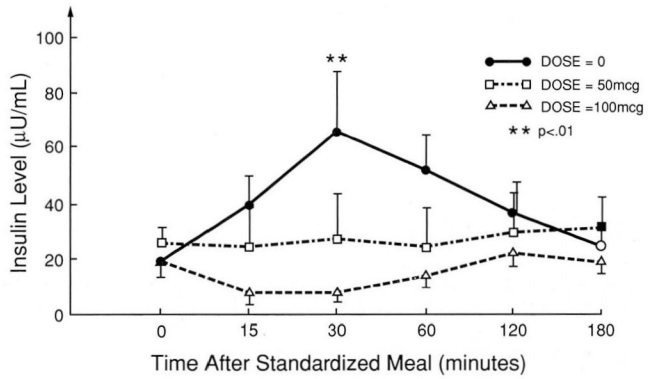

FIGURE 1. The effect of a SC injection of SMS 201-995 on insulin levels when given simultaneously with a standardized meal.

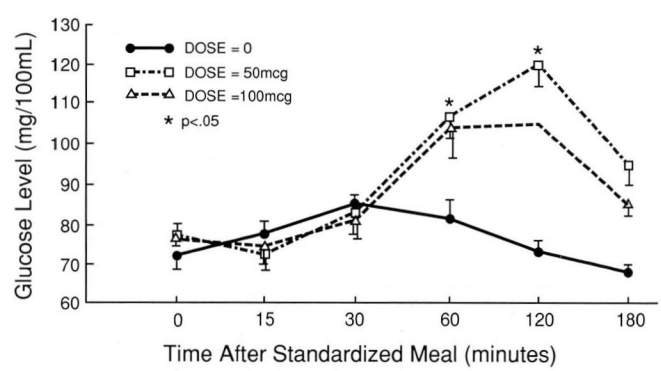

FIGURE 2. The effect of a SC injection of SMS 201-995 on glucose levels when given simultaneously with a standardized meal.

Synthesis of clinically useful SRIF analogs resulted in SMS 201-995 (Sandostatin). Bauer et al[7] reported that this analog was 45 times more active than SRIF in its inhibition of growth hormone (GH) secretion. The longer and more potent inhibitory effect is due to the greater resistance of SMS 201-995 to degradation. SMS 201-995 has been used in a variety of clinical settings including acromegaly, gastrointestinal bleeding, secretory diarrhea, pancreatic endocrine tumors, and Type I diabetes mellitus.[4]

Results of an open pilot study of SMS 201-995 in the treatment of psoriasis are reported in this volume.[8] Because mild diabetes mellitus may occur in states of somatostatin excess (somatostatinoma),[9] we also investigated in this study the effects of a standardized meal on glucose metabolism and levels of insulin, glucagon, and pancreatic polypeptide. Earlier reports showed a dose-related elevation of postprandial glucose in normal human volunteers exposed to a single IV bolus or 5 days of twice daily subcutaneous doses of SMS 201-995. We wondered whether carbohydrate intolerance continued during chronic administration of SMS 201-995. We also studied the pharmacokinetics of the drug during the meal and over a 24-hour period during chronic administration to determine if the absorption from subcutaneous sites and the metabolism of SMS 201-995 in psoriatic patients were similar to those in normal volunteers. Finally, because SRIF has been reported to suppress TSH, we measured TSH, T4, and T3 uptake in order to assess the risk of patients developing hypothyroidism.

PATIENTS AND METHODS

Nine adult male and female patients (aged 27 to 48 years) with chronic plaque psoriasis involving 10% or more of body surface were studied. The investigations were approved by the institutional human subjects committee, and informed consent was obtained from all patients. Liver and kidney function tests were normal in all patients, and there were no signs of diabetes mellitus. All systemic therapy specifically aimed at psoriasis was terminated 4 weeks before starting SMS 201-995. Patients were admitted to the Clinical Research Center at the Ohio State University Hospital. Following an overnight fast, blood samples for gut hormones were drawn at 0, +15, +30, +60, +120, and +180 minutes after a standardized breakfast, which consisted of two poached eggs, 1/2 cup orange juice, 1 slice toast, 1 tsp margarine, salt/sugar substitute, and decaffeinated tea (26.6 g carbohydrates, 15.3 g protein, 15.9 g fat, 311 calories).

SMS 201-995 was administered SC into uninvolved skin at a dose of 50 μg every 12 hours for 12 weeks beginning after the baseline studies. If the patient's psoriasis was clinically unchanged or had worsened at 4 weeks, the SMS 201- 995 dose was increased to 100 μg SC every 12 hours. The site of the self-administered injection was rotated among the abdomen, hip, and thigh. At 1, 4, 6, 8, and 12 weeks, overnight fasting blood samples were obtained after simultaneous injection of SMS 201-995 and ingestion of the standardized meal.

Blood samples were collected into chilled tubes of

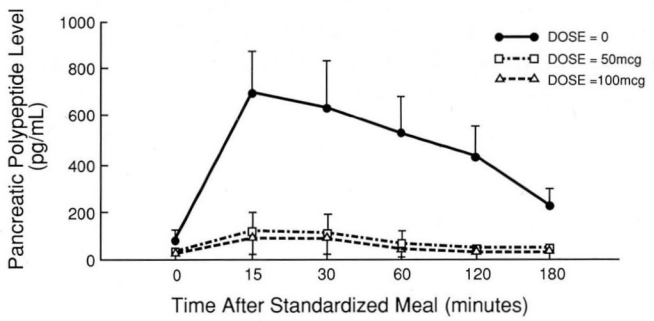

FIGURE 3. The effect of a SC injection of SMS 201-995 on pancreatic polypeptide when given simultaneously with a standardized meal.

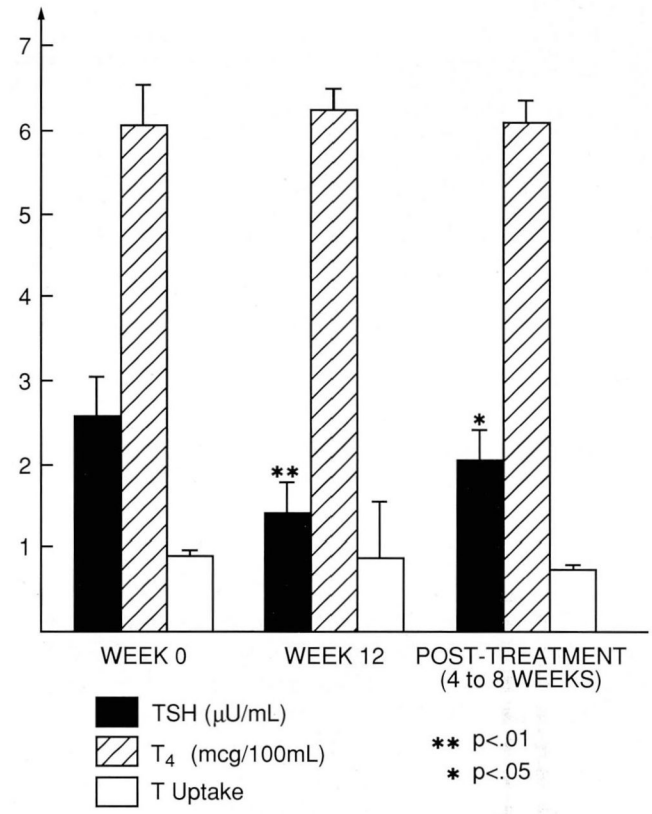

FIGURE 4. The levels of TSH, T4, and T3 uptake drawn at 0200 h before (week 0), during (week 12), and 4–8 weeks after chronic SC administration of 100–200 μg SMS 201-995 daily.

EDTA and centrifuged. The plasma was removed and stored at –20°C. SMS 201-995,[10] insulin, glucagon, pancreatic polypeptide (PP), TSH, and T4 were measured by specific radioimmunoassays (RIA), and T3 resin uptake (T3U) was measured by direct quantitation. The glucose was measured using a standard glucose oxidase method adapted for an autoanalyzer.

Analysis of variance (ANOVA) was performed for insulin, glucagon, glucose, and PP for each dose level (0, 50, 100 μg) separately over time. Comparisons between dose levels were made when there were sufficient degrees of freedom to test for interactions of time and dose. Multiple comparisons of means of each time point for each dose level were performed. TSH, T4, and T3 uptake were analyzed by paired t-tests. *P* values of ≤ .05 were considered statistically significant. The data are expressed as the mean ± SE.

RESULTS

The effects of SMS 201-995 given SC simultaneously with the standardized meal are shown in *Figures 1–4*.

The postprandial insulin peak response at 30 minutes was markedly blunted from 65.8 ± 11 μU/mL without treatment to 26.7 ± 8.6 μU/mL ($P \leq .01$) and 7.7 ± 2 μU/mL ($P \leq .01$) after the 50- and 100-μg doses, respectively (*Figure 1*). The insulin response at 120 and 180 minutes with treatment approached the values obtained at baseline. No delayed insulin response for the 50-μg and 100-μg doses was detected for as long as 180 minutes postprandially.

Mean glucose levels during insulin suppression were significantly elevated (*Figure 2*). There was no difference in the glucose levels from 0 to 30 minutes with and without treatment. At 60 minutes, however, the glucose level was elevated to 6.0 ± 0.28 mmol/L (108 ± 5.0 mg/dL) ($P \leq .05$) and 5.86 ± 0.40 mmol/L (105.6 ± 7.2 mg/dL) ($P \leq .05$) after the 50-μg and 100-μg doses, respectively. Without treatment the level was 4.6 ± 0.28 mmol/L (82.7 ± 5 mg/dL). The glucose levels peaked at 120 minutes with treatment and then declined. At 180 minutes they were still higher than the values obtained without treatment, although the difference was not statistically significant.

In four subjects, glucagon was measured before and after the 50-μg dosage of SMS 201-995. No significant meal-time interaction or effect due to treatment with SMS 201-995 was found.

The suppressive effect of SMS 201-995 on PP post-

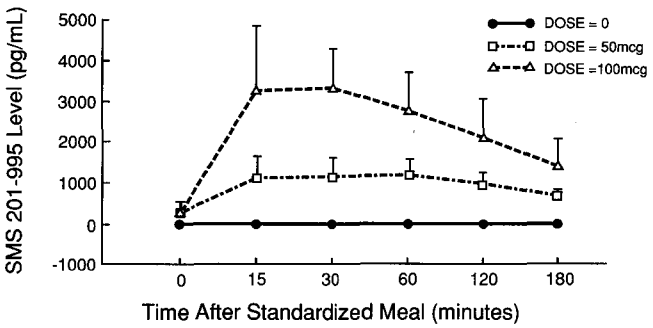

FIGURE 5. The level of SMS 201-995 measured after the simultaneous SC administration of a 50- or 100-μg dose with a standardized meal. SMS 201-995 is undetectable in untreated patients.

prandially (*Figure 3*) was noted at 15 minutes with values of 103.2 ± 39.6 pg/mL ($P \leq .05$) and 91.0 ± 43 pg/mL ($P \leq .05$) for the 50-μg and 100-μg doses, respectively, compared with 692.5 ± 91.3 pg/mL without treatment. The dramatic PP suppression continued equally for both doses for the entire 180 minutes postprandially. In addition, when patients were given SMS 201-995 4 hours prior to the standardized meal, marked suppression of PP levels was observed for both doses (data not shown).

The nocturnal (0200 h) TSH rise was blunted after 12 weeks of treatment from 2.54 ± 0.53 μU/mL to 1.38 ± 0.38 μU/mL ($P \leq .01$). The TSH level was still significantly depressed at 2.02 ± 0.45 μU/mL ($P \leq .05$) 4–8 weeks after treatment. T4 and T3U were normal at baseline and were not significantly altered by treatment through 12 weeks or 4–8 weeks after treatment (*Figure 4*). Only eight of the nine patients were included in the statistical analysis because one patient was receiving thyroid hormone replacement therapy.

The mean peak plasma concentration of SMS 201-995 (*Figure 5*) of 1214.5 ± 230.4 pg/mL and 3337.1 ± 479.1 pg/mL for 50-μg and 100-μg doses, respectively, was reached 30 minutes after SC injection. The levels fell to 676.8 ± 100.6 pg/mL and 1475.8 ± 316.3 pg/mL for the 50-μg and 100-μg doses, respectively, over the following 150 minutes of measurement. During the 24-hour measurement, samples were obtained every 2 hours. SMS 201-995 rose to 1322 ± 162.8 pg/mL and 2619.1 ± 251.2 pg/mL (50-μg and 100-μg doses, respectively) 2 hours after the 2000 h injection then fell progressively to 178.5 ± 24.1 pg/mL and 198.2 ± 108.8 pg/mL (50-μg and 100-μg doses, respectively) by 0800 h the next morning. The half-life of SMS 201-995 was calculated to be 139 and 128 minutes for the two doses, consistent with previous reports.

DISCUSSION

We have examined the effects of SMS 201-995 on insulin, glucagon, glucose, and PP after a standardized meal, and nocturnal (0200 h) TSH, T4, and T3U levels after 0 and 12 weeks of treatment and 4–8 weeks posttreatment.

Somatostatin has also been shown to inhibit glucagon and growth hormone,[11] diminish gut motility, delay gastric emptying, prolong transit time in the small intestine, and reduce nutrient absorption.[2,4] All of these effects may lower blood glucose. The insulin response in our patients was blunted and was sufficient to cause significant glucose elevation after the standardized meal. Despite the dramatic inhibition of insulin secretion observed in this study, only mild glucose elevation resulted. Glucagon and growth hormone probably did not play a major role in the genesis of hyperglycemia. Glucagon levels were measured in four subjects and were unaffected by either the ingestion of the standardized meal or the 50-μg dose of SMS 201-995. While we did not measure GH after the meal, it is known that hyperglycemia suppresses GH. We were unable to show statistically significant GH depression at any time during treatment in 24-hour pooled serum specimens drawn every 2 hours.[8] Therefore, we conclude that carbohydrate intolerance in these subjects was caused by inhibition of insulin release. This effect may have been diminished by decreased and/or delayed carbohydrate absorption.

A circadian rhythm in the plasma concentration of TSH is present in adults. TSH levels have been shown to peak at levels twice as high at night, between 2115 and 0530 hours, as during the day.[12,13] It has been reported that SMS 201-995 has no effect on basal TSH although these studies were performed during the day when TSH levels are at their limit of sensitivity in many assays.[14] Another study demonstrated TSH suppression during a 2-hour (0100 h to 0300 h) infusion of SRIF.[3] Our data confirm this nocturnal TSH suppression, which persisted in our study for at least 4 weeks after the treatment was terminated. The T4 and T3U showed no depression during and after the SMS 201-995 treatment. Barkan et al[15] found no change in T4 and T3U resin uptake in 8 acromegalics treated with SMS 201-995 for 1–2 months. However, both basal TSH and responses to

TRH were significantly inhibited. It has been hypothesized that prolonged suppression of TSH by SRIF may decrease the secretion of T4 and T3 thereby leading to hypothyroidism.[3] Nevertheless, all of our patients and those of Barkan et al[15] remained chemically and clinically euthyroid throughout the study period.

PP is found predominantly in D2 cells in the pancreatic islets. Vagally-mediated stimuli, such as food in the gut and hypoglycemia, can cause the release of PP although its actions in humans are uncertain.[16] SMS 201-995 demonstrated a potent, rapid, and long-acting postprandial inhibitory effect on PP. Both doses employed appeared to suppress PP maximally, indicating that PP is highly sensitive to the effects of SMS 201-995. The clinical significance of suppression of PP in psoriatic patients is unknown.

SRIF has been shown to have a short half-life (1.1–3 minutes) and a rapid plasma disappearance necessitating intravenous administration.[17] SMS 201-995, in this study, was rapidly absorbed from any SC injection site, peaked in plasma at 30 minutes, and then decayed slowly with a half-life of greater than 2 hours for both the 50-μg and the 100-μg doses. These results are comparable to those obtained in normal volunteers,[18,19] rendering it a clinically useful analog of SRIF in the treatment of psoriasis.

For results of the clinical study, see Camisa et al[8] (pp 71–76 in this issue).

The mechanism of action of SMS 201-995 in psoriasis is not known. In this open study, it is not possible to state whether postprandial hyperglycemia due to inhibition of insulin release, suppression of postprandial PP release, and suppression of nocturnal TSH observed during chronic daily administration of 100 or 200 μg SMS 201-995 helped to cause the modest improvement of the skin disease noted in our patients.

SMS 201-995 appears to be a safe, well-tolerated treatment that may be efficacious in psoriasis. However, confirmation of efficacy will have to await the completion of multicenter double-blind placebo-controlled trials currently in progress.

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