Reduction of pituitary size by the somatostatin analogue SMS 201-995 in a patient with an islet cell tumour secreting growth hormone releasing factor

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Abstract. Acromegaly is rarely caused by the ectopic secretion of growth hormone releasing factor (GRF) from peripheral neuroendocrine tumours. We evaluated the ability of a recently developed somatostatin analogue (SMS 201-995, Sandoz) to reduce hormone levels and pituitary size in a young woman with acromegaly and Zollinger-Ellison syndrome secondary to a metastatic pancreatic islet cell tumour secreting GRF and gastrin. Gastrin, GRF, and growth hormone (GH) levels declined dramatically following the initiation of therapy with the analogue by continuous iv infusion. Although intermittent sc therapy was not effective in suppressing hormone levels, continuous sc infusion of SMS 201-995 has provided good control of both GRF and GH levels for nine months. Moreover, treatment with SMS 201-995 was associated with a substantial reduction in pituitary enlargement and an improvement in her gastric symptoms. Continuous sc infusion of SMS 201-995 may be useful in treating enlarged pituitaries resistant to other modes of therapy.

Classical acromegaly is thought to be the result of autonomous secretion of growth hormone (GH) from a pituitary adenoma. While surgical removal of GH-secreting adenomas often results in reduction in GH and somatomedin-C levels and in an amelioration of the symptoms associated with acromegaly, clinical and biochemical relapses are common. Acromegaly may also occur in patients with neuroendocrine tumours that ectopically secrete GH-releasing factor (GRF) (Frohman et al. 1980; Thorner et al. 1982; Guillemin et al. 1982; Scheithauer et al. 1984; Vance et al. 1985; Wilson et al. 1984). These patients also have enlarged pituitary glands, suggesting that the elevated GRF levels induced pituitary hyperplasia or adenoma formation. Therapy for the ectopic GRF syndrome is best directed at the primary neuroendocrine tumour, where surgical removal may completely cure the acromegaly. If the primary tumour is not resectable, however, treatment of the GH excess can be very difficult. Since the pituitary hyperplasia is diffuse, total hypophysectomy may be necessary.

Unfortunately, medical therapy for classical acromegaly using bromocriptine or other ergot derivatives has proved to be of only limited long-term benefit. Recently, however, investigators have reported acute (Ch'ng et al. 1985; Lamberts et al. 1985a) and long-term (Lamberts et al. 1985b) reductions in GH levels in acromegalic patients following therapy with the potent somatostatin analogue, SMS 201-995. We therefore were encouraged to examine the effects of SMS 201-995 in a patient with a metastatic islet cell carcinoma which produces both GRF and gastrin.

Methods

Patient

The patient is a 27 year old woman who presented at 19 years of age with the Zollinger-Ellison syndrome secondary to a metastatic pancreatic islet cell tumour. The
details of her clinical history have been reported (Wilson et al. 1984). Multiple courses of chemotherapy were unsuccessful in reducing either tumour growth or gastrin secretion. Severe abdominal pain necessitated high dose cimetidine and, later, ranitidine therapy. By age 25, typical acromegalic facies were apparent, and the patient noted severe hyperhidrosis. Plasma levels of GH and GRF were consistently elevated and computerized tomography (CT) of the cranium revealed an enhancing non-homogeneous mass within an enlarged sella turcica. As the patient was unable to tolerate bromocriptine because of severe gastric discomfort, we began therapy in 1984 with SMS 201-995 with the expectation of decreasing both tumour and pituitary hormone secre-
tion. Informed consent was obtained from the patient and all studies were approved by the Stanford Committee for the Protection of Human Subjects.

**Drug**

SMS 201-995, an octapeptide analogue of somatostatin, was provided by Sandoz Ltd. (Basel, Switzerland). This analogue inhibits growth hormone secretion more readily than insulin secretion in animal models and has a substantially longer half-life than native somatostatin (Bauer et al. 1982). It has been used to inhibit hormone secretion from a variety of neuroendocrine tumours.

**Samples**

Samples for hormone assay were initially obtained every 30 to 60 min during the continuous intravenous infusion of SMS 201-995, and every 8 h thereafter in the hospital. Samples were subsequently obtained at 10.00 h during monthly out-patient visits. A standard TRH test was performed by infusing 400 µg iv and obtaining serum samples at 0 and 30 min.

**Assays**

GRF (1–40) levels were determined by radioimmunoassay (Wilson et al. 1984) using anti-human GRF (1–44) amide antisera, GRF (1–40) standards, and iodine-125-
GRF (1–40) as radioligand provided by Peninsula Laboratories (Belmont, CA). This assay has a lower limit of sensitivity, defined as 15% of maximum displacement, of 0.009 ng/ml. The normal range for plasma GRF is less than 0.02 ng/ml.

GH (National Hormone and Pituitary Program, normal < 10 ng/ml), gastrin (Becton-Dickinson, Orangeburg, NY, normal range < 100 pg/ml), insulin-like growth factor I (IGF-I, also known as somatomedin-C) (normal range 120–244 ng/ml), and IGF-11 (normal range 370–952 ng/ml) levels were determined by specific radioimmunoassays (Wilson et al. 1982).

**Results**

Mean hormone levels prior to therapy were 191 ng/ml for GH, 5.50 ng/ml for GRF, and 5025 pg/ml for gastrin. Immediately following initiation of a continuous intravenous infusion of 25 µg/h of SMS 201-995, levels of these hormones fell rapidly (Fig. 1). The initial rate of decline for all three hormone levels (logarithm of concentration versus time) was linear for the first 120 min. The calculated half-lives were 30 min for GH, 84 min for GRF, and 78 min for gastrin. Three hours later, the rate of the infusion was increased to 50 µg/h for the following 21 h. Hor-

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**Fig. 1.**

Initial gastrin (upper), GH (middle), and GRF (lower) response to therapy with the somatostatin analogue. Hatched boxes represent continuous iv SMS 201-995 therapy (25 µg/h for 3 h and 50 µg/h for 21 h) and arrows indicated intermittent subcutaneous injections (50 µg/dose). Hours of infusion are noted on the X-axis.
mone levels remained suppressed (mean plateau levels (h 7–16), GH: 13 ng/ml, GRF: 0.56 ng/ml, and gastrin: 486 pg/ml) until h 17 when levels of all three hormones rose, possibly secondary to either an undetected interruption in the infusion or break-through hormone secretion despite ongoing SMS 201-995 therapy. Subsequently, levels of all three hormones decreased again. Mean hormone levels during the pre-treatment and plateau (from 7 to 16 h) periods are shown in Fig. 2. Although the patient had no discomfort during the initial infusion of 25 µg/h, she reported moderate nausea and gastric discomfort 9 h after the dose was increased to 50 µg/h.

Following 24 h of continuous intravenous therapy, SMS 201-995 was given by intermittent sc injection, 50 µg three times a day. Levels of all three hormones were poorly suppressed (mean levels; GH: 292 ng/ml, GRF: 2.7 ng/ml, and gastrin: 2112 pg/ml) and were quite variable, indicating that the analogue did not suppress hormone levels for the full interval between injections (Fig. 1). Therapy was subsequently changed to a continuous sc infusion at a rate of 21 µg/h (500 µg/day) of SMS 201-995 using a portable infusion pump (Minimed, Pacesetter Systems, Inc., Sylmar, CA). During the first nine months of this therapy, there was a decrease in the mean levels of GH (19 ng/ml), GRF (1.14 ng/ml), and gastrin (1248 pg/ml). The variability in hormone levels, as measured by the standard deviation, was also decreased when compared with intermittent sc therapy (Fig. 2).

The effects of the different methods of administering SMS 201-995 on IGF-I and IGF-II levels are shown in Table 1. Mean IGF-I levels during the continuous sc infusion of SMS 201-995 were significantly lower than that found in the baseline period (P = 0.0381, one tailed Student's t-test), although they remain at the upper limit of the normal range.

While on continuous sc SMS 201-995, the patient’s GH level increased from 5 to 300 ng/ml 30 min after an iv bolus of 400 µg of TRH. While this rise is clearly abnormal, it represents a distinct change in her response to TRH prior to analogue therapy (450 to 6190 ng/ml).

In addition to clear decreases in gastrin, GRF and GH levels, the patient had a definite decrease in the size of her enlarged pituitary following SMS 201-995 therapy as assessed by serial cranial CT scans. Initial scans revealed a large suprasellar mass, abutting the optic chiasm, although the patient’s visual field examination was normal. There was a 20% reduction in the volume of the pituitary following six weeks of continuous sc therapy and a 30% reduction in pituitary volume was observed following six months
of therapy. The patient, who had secondary amenorrhoea with hypogonadotrophic hypogonadism since the discovery of her tumour, observed the return of monthly ovulatory menses after 9 months of therapy. No substantial change in the size of the intraabdominal tumour or metastases could be detected on abdominal CT scan, however.

Although gastrin levels remain elevated, the patient has been able to reduce her dose of ranitidine without any increase in her gastric discomfort. In addition, she has noted a dramatic reduction in her other symptoms, including hyperhidrosis and fatigue. No side effects from the medication have been noted; in particular, the patient has had normal bowel movements without nausea or vomiting. She has been able to return to college and to pursue a moderately vigorous exercise programme. Of note, she reports a marked increase in gastric distress and perspiration whenever the SMS 201-995 infusion is interrupted for more than one h.

### Table 1.

Somatomedin levels during therapy with SMS 201-995.

<table>
<thead>
<tr>
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<th>n</th>
<th>IGF-I (ng/ml) mean ± SD</th>
<th>IGF-II (ng/ml) mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3</td>
<td>431 ± 86</td>
<td>895 ± 178</td>
</tr>
<tr>
<td>End of continuous iv infusion</td>
<td>1</td>
<td>373</td>
<td>738</td>
</tr>
<tr>
<td>Intermittent sc therapy</td>
<td>4</td>
<td>398 ± 88</td>
<td>1293 ± 342</td>
</tr>
<tr>
<td>Continuous sc therapy</td>
<td>3</td>
<td>241 ± 99*</td>
<td>818 ± 49</td>
</tr>
</tbody>
</table>

Normal values (mean ± 2 s.d) for adults: IGF-I, 120–244 ng/ml; IGF-II, 370–952 ng/ml. Samples were obtained 2 days, 3 days, 1 month, and 2 months following initiation of intermittent sc therapy. Samples were obtained 1, 2, and 6 months following initiation of continuous sc therapy.

* Significantly less than baseline, *P* = 0.0381, one-tailed *t*-test.

Discussion

The potent inhibitory effects of native somatostatin on GH secretion have been demonstrated in short term studies in acromegalic patients (Besser et al. 1974). Attempts to use native somatostatin as a therapeutic agent, however, have been limited by its extremely short half-life. The somatostatin analogue SMS 201-995 appears to circumvent this difficulty and has been successful in reducing GH levels in patients with classical acromegaly (Ch'ng et al. 1985; Lamberts et al. 1985b) and with GRF-secreting tumours (von Werder et al. 1984; Vance & Thorner 1985).

With our subject, continuous iv infusion of SMS 201-995 resulted in prompt decreases in GH, GRF, and gastrin levels. The half-life of GRF in our subject was longer than the reported mean value in normal adult males (Frohman et al. 1984), suggesting that GRF secretion was not completely suppressed by SMS 201-995. GH levels fell most rapidly with a half-life of 30 min, consistent with nearly complete suppression of secretion. Since this suppression of GH secretion occurred at a time when GRF levels were still elevated well above normal, it is clear that SMS 201-995 has direct effects both on the pituitary to decrease GH secretion and on the islet cell tumour to decrease GRF and gastrin secretion.

After the SMS 201-995 therapy was changed to intermittent sc injections, the subject complained of an increase in gastrointestinal symptoms, and hormone secretion from the tumour was not suppressed throughout the inter-dose interval. The mean GH level during this mode of therapy was as high as that found during the baseline period, indicating that GH levels were rebounding above pre-treatment levels between injections. Rebound elevation of GH levels has been demonstrated in acromegals following short-term therapy with somatostatin (Besser et al. 1974). Von Werder et al. (1984) were able to suppress GRF levels for over 8 h in a patient similar to ours with intermittent sc SMS 201-995. Vance et al. (1985), however, were able to suppress GRF and GH
levels for only 5 to 6 h in another such subject following sc injections of SMS 201-995. With the use of a continuous sc infusion of SMS 201-995, GH levels were suppressed close to the normal range. The persistently elevated IGF-I levels and the abnormal GH response to TRH indicate, however, that the acromegaly has not been completely cured. Only moderate suppression of gastrin and GRF levels was achieved. IGF-I levels remained within the normal range. In addition, there was a 20% decrease in pituitary volume after just 6 weeks of SMS 201-995 therapy. This reduction in size may have been mediated by a direct pituitary effect of SMS 201-995 and also in part by the reduction in the levels of the trophic tumour product, GRF. This decrease in pituitary mass is similar to that described in some subjects with GH and prolactin secreting pituitary adenomas following treatment with bromocriptine (Wass et al. 1979). While it is possible that spontaneous infarction of the pituitary could account for the change in size, we believe that this is unlikely in view of the return of menses and the maintenance of other pituitary functions; there has been no sign of pituitary apoplexy. The use of SMS 201-995 in the treatment of large pituitary adenomas resistant to other modes of therapy deserves further investigation in light of the observation that long-term administration was associated with a reduction in pituitary volume in this acromegalic patient.

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References


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