Effect of a Single Administration of Somatostatin Analogue (SMS 201-995) on GH, TSH and Insulin Secretion in Patients with Acromegaly

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Abstract

The effect of a long-acting somatostatin analogue SMS 201-995 on GH secretion was investigated. Eleven acromegalic patients received a single dose of 50 μ g SMS 201-995 administered subcutaneously, and plasma GH, IGF-I, GRF, TSH, IRI and blood glucose were determined at regular intervals. Nine of 11 patients had elevated basal plasma GH levels above 5 ng/ml. In all patients, plasma GH levels fell immediately from 39.5 ± 17.3 ng/ml (mean $\pm$ SEM) to 4.3 ± 1.6 ng/ml ($P < 0.05$) with a maximal inhibition of $82.9 \pm 3.3\%$ of the basal levels and the suppression persisted for about 6 h of the observation period.

IGF-I and GRF levels were not apparently altered. TSH and IRI levels also rapidly fell. Blood glucose levels fell slightly by 0.5 h. Ten of 11 patients had pain at injection sites. Except for this, no side effects were observed. Our results show that the new somatostatin analogue SMS 201-995 may inhibit GH hypersecretion in acromegalic patients for significant periods, suggesting that this agent can be a useful clinical tool for the treatment of acromegaly.

A long-acting somatostatin analogue (SMS 201-995; Sandoz, Basel, Switzerland) was developed (Bauer *et al.*, 1982 a, b) and became available for the treatment of acromegaly recently. The subcutaneous administration of this peptide has produced a clear reduction in plasma GH of long duration in acromegalic patients including those whose plasma GH levels were not suppressed below 5 ng/ml by any other treatment. This analogue was reported to show less rebound hypersecretion of GH

than the natural somatostatin (Besser *et al.*, 1974; Ch'ng *et al.*, 1985; Lamberts *et al.*, 1985 a, b; Plewe *et al.*, 1984 a).

We have studied here the effect of a single subcutaneous administration of 50 μ g SMS 201-995 in 11 acromegalic patients to see if this new drug could be suitable for the clinical management of acromegaly.

Materials and Methods

The patients with acromegaly consisted of 3 males and 8 females aged 34-68 years. The

Table 1. Clinical and laboratory data in 11 patients with acromegaly

Patient No.	Age (ys)	Sex (M/F)	Previous Treatment	Present Treatment	Basal GH ng/ml	Basal IGF-I ng/ml
1*	34	F	Op	BR + T ₄ + F	60.6	64.8
2	34	F	Op + Rx	BR	20.0	64.0
3*	35	M		BR	81.0	205.0
4	44	F	Op + Rx	T ₄ + F	195.0	160.0
5*	52	F	Op + Rx + BR	Lisuride® + T ₄ + F	30.0	222.5
6	54	M	BR		5.0	172.0
7	54	F		BR	19.5	126.0
8	66	M		BR	8.1	116.0
9	66	F	Op	PTU	1.1	110.0
10*	66	F	Op		5.0	27.2
11	68	F	BR		9.5	77.2
Mean	52.1				39.5	128.0
SD	13.6				57.4	62.5
SEM	4.1				17.3	19.8

Transsphenoidal surgery (Op), Irradiation (Rx), Bromocriptine (BR), Thyroxine (T₄), Hydrocortisone (F), Propylthiouracil (PTU). *Diabetic Patients.

diagnostic criteria were nonsuppressibility of elevated plasma GH below 5 ng/ml in response to an oral 75 g glucose load in addition to the clinical picture. One patient (case 9) had hyperthyroidism with a high level of TSH and was suspected to have combined TSH producing pituitary tumor. Informed consent was obtained from each patient and the experimental protocol was approved by the Human Subjects Investigation Committee of our department. The clinical and laboratory data for these patients are shown in Table 1. Six of 11 patients had previously been treated by transsphenoidal surgery and 3 of them had additional irradiation. Five of the rest have been treated with bromocriptine. Basal plasma GH levels ranged 1.1–195.0 ng/ml with a mean of 39.5 ± 17.3 (mean $\pm$ SEM) ng/ml. Plasma IGF-I levels varied between 27.2 and 222.5 ng/ml with a mean of 128.0 ± 19.8 ng/ml. Bromocriptine and Lisuride® therapy was withdrawn the day before the investigation.

All patients were studied under resting conditions. They received 50 μ g SMS 201–995 subcutaneously around 0830 h to 0930 h. Each subject was fitted with a heparin-locked cannula in a forearm vein for drawing blood. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after injection for the determination of plasma GH, insulin-like growth factor I (IGF-I), GRF, TSH, immunoreactive insulin (IRI) and blood glucose.

In one patient blood samples were taken in addition at 8 and 12 h. Four hours after injection, the cannulae were withdrawn and the patients had a meal provided by the hospital.

SMS 201–995 was kindly provided by Sandoz (Basel, Switzerland). Plasma GH was determined by a double antibody radioimmunoassay (RIA) generously provided by the National Hormone and Pituitary Program of NIADDK, NIH (hGH: AFP-4793B; antibody: AFP-97720133). Plasma GH levels below 1 ng/ml were measured by immunoradiometric assay kit (IRMA; Boots-Celltech Diagnostic Limited, Berkshire, U. K.). The minimal plasma GH detected by IRMA was 0.05 ng/ml. Plasma IGF-I was measured by RIA (Miyakawa *et al.*, 1986) with modification of the method of Furlanetto *et al.* (1977). The normal range for human adults and the range for hypopituitarism in this assay were 9.2–35 ng/ml and <1–6.1 ng/ml, respectively. Plasma GRF was determined by RIA described by Shibasaki *et al.* (1984). TSH was determined by immunoradiometric assay (IRMA; Boots-Celltech Diagnostic Limited, Berkshire, U. K.) provided by Special Reference Laboratory (Tokyo, Japan). The minimal detectable serum TSH was 0.1 μ U/ml. Serum IRI was measured with a commercially available RIA kit (Dinabot Co., Ltd.). Blood glucose was measured by the glucose-oxidation method.

Paired *t*-test and Student's *t*-test was used to determine the statistical significance.

Results

Plasma GH levels after 50 µg subcutaneous administration of SMS 201-995 are shown in

Table 2 and Fig. 1. In all patients, plasma GH levels rapidly fell from 39.5 ± 17.3 ng/ml (mean $\pm$ SEM) to 4.3 ± 1.6 ng/ml ($P < 0.05$) after injection. The maximal inhibition of the GH level was reached at 2-5 h with a mean inhibition of $82.9 \pm 3.3\%$ of the basal level, and the GH level was still suppressed to $68.1 \pm 7.2\%$ at 6 h after injection. In

Table 2. Plasma GH (ng/ml) levels after 50 µg sc administration of SMS 201-995

Patient No.	Hours after SMS 201-995 Administration									
	0	0.5	1	1.5	2	3	4	5	6 h	
1	60.6	32.8	16.2	8.8	5.7	—	4.3	—	9.8	
2	20	10.2	5.1	4.6	3.3	4.7	3.2	4.5	4.7	
3	81	32	20	12.1	6.4	4.5	6.4	11.1	19.3	
4	195	85	57.5	37	19	27.5	25.5	20.5	26.5	
5	30	18	9.5	5.5	4.6	3.2	2.6	5.8	6.9	
6	5	2.7	1.7	1.3	0.7	0.7	0.9	1.1	1.2	
7	19.5	9.2	6	4.5	3.5	3.4	3.5	3.2	—	
8	8.1	5.3	3.4	2.7	2.3	2.4	2.5	4.7	5.8	
9	1.1	0.6	0.5	0.5	0.5	0.4	0.5	0.7	0.7	
10	5.0	2.0	1.2	0.8	0.7	0.7	1.1	1.1	2.7	
11	9.5	4.3	2.3	1.4	0.9	0.7	0.6	0.6	0.6	
Mean	39.5	18.4	11.2	7.2	4.3	4.8	4.7	5.3	7.8	
SD	57.4	24.9	16.6	10.5	5.3	8.1	7.1	6.2	8.1	
SEM	17.3	7.5	5.0	3.2	1.6	2.6	2.2	2.0	2.7

Fig. 1. Percent decrease in GH after a single administration of SMS 201-995 in acromegalic. The numbers in the figure correspond to the patients listed in Table 1.

Fig. 2. Plasma GRF and IGF-I levels after a single administration of SMS 201-995 in 10 acromegalic patients.

Fig. 3. Serum TSH levels after a single administration of SMS 201-995 in 9 acromegalic patients.

one patient (No. 10) the GH level was followed for 12 h. In this case, the GH levels fell from 5 ng/ml to 0.7 ng/ml within 2 h and rose to 7 and 25 ng/ml at 8 and 12 h after injection, respectively.

Plasma GRF and IGF-I levels after SMS 201-995 administration are shown in Fig. 2. IGF-I and GRF, with a basal concentration of 128.0 ± 19.8 ng/ml and 12.9 ± 1.0 pg/ml, respectively, showed no significant change.

Serum TSH levels after SMS 201-995 administration are shown in Fig. 3. The serum TSH level was suppressed to about 50% of the basal level for 2-4 h after injection. One patient (No. 9) with high basal TSH level showed a significant reduction in TSH from 18.0 μ U/ml to 6.0 μ U/ml at 6 h.

Serum IRI and blood glucose levels after SMS 201-995 administration are shown in Fig. 4. The IRI level immediately fell from 26.2 ± 6.5 μ U/ml to 7.1 ± 1.2 μ U/ml and was lowest at 0.5 h after injection. IRI levels gradually rose after 2 h, but were suppressed to $44.6 \pm 4.1\%$ of basal levels at 4 h after injection. Blood glucose levels did not change significantly.

Ten of 11 patients complained of pain at the injection site, which persisted for a few minutes. No tumor or redness has remained at the site. No other side effects were observed.

Fig. 4. Serum insulin and glucose levels after a single administration of SMS 201-995 in 10 acromegalic patients.

Discussion

After a single subcutaneous administration of 50 μ g SMS 201-995, plasma GH levels were strongly suppressed below 5 ng/ml up to 6 h in 10 of 11 patients, whereas one patient (No. 4), whose basal GH level was 195 ng/ml had a minimum GH value of 20.5 ng/ml, showing about a 90% reduction of the initial level. These results were compatible with the results of other workers (Althoff *et al.*, 1984; Ch'ng *et al.*, 1985; Mayer and Tillil, 1984; Lamberts *et al.*, 1985 a, b; Plewe *et al.*, 1984 a, b). This dose of 50 μ g SMS 201-995 corresponded to 0.44–1.06 μ g/kg body weight in each patient. There seemed to be no relationship between the inhibition of GH secretion and the SMS 201-995 dose per body weight used.

No acute effect of SMS 201-995 on plasma IGF-I was observed. These data suggest that there is no direct inhibitory effect of SMS 201-995 on IGF-I secretion. Plewe *et al.* (1984 c, d) reported that IGF-I levels were reduced with three times a day subcutaneous injection of 50 μ g SMS 201-995 over a 3-day period. More recently, Lamberts *et al.* (1985a) reported that after long term treatment, plasma IGF-I levels

were significantly decreased in 4 acromegalic patients. As these reports have shown, long term administration of SMS 201-995 is necessary to obtain a decrease in IGF-I.

Plasma GRF levels were not altered during 6 h of investigation. A single injection of 50 μ g SMS 201-995 seems to have no effect on GRF secretion. On the other hand, Bloom *et al.* (1984) and Von Werder *et al.* (1984) reported that chronic administration of SMS 201-995 was effective in lowering plasma GRF levels in patients with GRF-producing tumors.

Serum TSH levels were suppressed in all patients including one patient (No. 9) who had a high basal TSH level. This result shows that the SMS 201-995 administration is also effective in reducing hypersecretion of TSH.

The suppression by SMS 201-995 of insulin secretion in our acromegalic patients was strong and continued for up to 4 h of the study period while the blood glucose did not change significantly, but had decreased slightly by 30 min after SMS 201-995 injection and gradually increased by 4 h. Blood glucose is regulated by many factors such as insulin, glucagon, and hGH, and also controlled by somatostatin (Clements and Elias, 1985; Kraenzlin *et al.*, 1985; Schultze *et al.*, 1983; Spinas *et al.*, 1984).

In this study, we have not determined the glucagon levels. Our observations on the blood glucose profile might be the result of a combination of these factors.

We conclude that SMS 201-995 is a potent somatostatin analogue in suppressing the GH secretion in acromegaly in the acute phase. However, the optimal dose, the optimal number of administrations, or a less painful injection route should be considered for the clinical management of acromegaly.

Acknowledgements

The authors are greatly indebted to Sandoz Pharmaceutical Co., Ltd. (Basel, Switzerland) for supplying somatostatin analogue, SMS 201-995.

This work was partly supported by Grants in Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (No. 61440052, No. 61570566, and No. 61770872), a Research Grant from the Intractable Disease Division, Public Health Bureau, Ministry of Health and Welfare, and a Research Grant from the Foundation for Growth Science in Japan.

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