

NOTE

## Preoperative Treatment of Growth Hormone-Producing Pituitary Adenoma with Continuous Subcutaneous Infusion of Octreotide

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**Abstract.** Preoperative therapy with octreotide, a long-acting somatostatin analog, suppresses GH hypersecretion, shrinks GH-producing tumors and leads to an improvement in subsequent surgical remission in acromegalic patients. A continuous infusion of octreotide has demonstrated more persistent suppression of GH secretion than intermittent injections, and only a few studies were reported on the effect of the tumor shrinkage with a continuous infusion of a small dose of octreotide. We therefore investigated the preoperative effects of small doses of octreotide (120–240  $\mu\text{g/day}$ ) administered continuously (with a subcutaneous infusion pump) over a short period (2 or 4 weeks) in nine untreated acromegalic patients. Octreotide therapy resulted in suppression of serum GH and IGF-1 concentrations in 8 out of 9 patients and reduction in pituitary tumor size measured by MRI in all patients (by 7.9 to 38.5%). In particular, considerable reduction in tumor size (more than 20%) occurred in 6 of 9 patients. In three patients assessed serially throughout the preoperative period, reduction in tumor size was noted within only one week after the start of octreotide therapy and reduction rate more than 20% was obtained within the first two weeks. In one patient, suprasellar tumor expansion totally disappeared after such therapy. Our results indicate that short-term continuous subcutaneous infusion of a small dose of octreotide results in not only inhibition of GH hypersecretion but also shrinkage of tumor size prior to surgery.

*Key words:* Acromegaly, Octreotide, Continuous subcutaneous infusion, GH, Tumor shrinkage  
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THE primary treatment for GH-producing pituitary adenomas is transsphenoidal surgical excision, but plasma GH levels are suppressed to below 5 ng/ml after surgery in only about 60% of patients with acromegaly [1–4]. On the other hand, the treatment with a long-acting somatostatin analog, octreotide, reduces GH hypersecretion in up to 90% of

acromegalic patients [5], and induces shrinkage of the tumor size in approximately 50% of GH-producing tumors [6, 7]. In fact, octreotide has been used for long-term management of acromegalic patients post-operatively [5]. In addition, several studies have shown the usefulness of octreotide administered preoperatively in producing shrinkage of the pituitary tumor, a process that also leads to improvement in the surgical remission rate in acromegalic patients [8–11].

Unfortunately octreotide has to be injected subcutaneously two or three times per day in order

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to produce an effective inhibition of GH secretion since a bolus injection of octreotide suppresses GH secretion for only 6–8 h [12, 13]. Furthermore, repetitive injections of a large daily dose (300 to 1,500  $\mu\text{g}/\text{day}$ ) for a long period (3 months to 3 years) [8–11] might reduce compliance in addition to the prohibitive costs and need for long-term management. On the other hand, continuous infusion of octreotide has demonstrated more persistent suppression of GH secretion than intermittent injections [14, 15], indicating that such a therapeutic regimen may allow a reduction in the total daily dose and the duration of treatment to produce tumor shrinkage, but only a few studies have been reported on the tumor shrinking effect with continuous infusion of a small dose of octreotide [15, 16].

In this prospective study, we investigated the changes in the size of pituitary tumors in nine patients with acromegaly treated with a small dose (120 or 240  $\mu\text{g}/\text{day}$ ) of octreotide administered preoperatively for a short duration (2 or 4 weeks), with a portable continuous infusion pump.

### Subjects and Methods

Nine newly diagnosed acromegalic patients (5 males and 4 females, aged 32 to 55 years,  $43 \pm 9$  years, mean  $\pm$  SD) were studied. They were hospitalized in the First Department of Internal Medicine, Nagasaki University School of Medicine, during a two-year period in 1995 and 1996. The nature of the study was fully explained to all the patients and their consent was obtained. The diagnosis of acromegaly was based on the

diagnostic criteria of the study section for hypothalamic-pituitary dysfunction supported by the Japanese Ministry of Health and Welfare. Pituitary tumors were detected in all patients on magnetic resonance imaging (MRI). The clinical characteristics are summarized in Table 1.

GH secretion was assessed by measuring blood samples at 0800, 1400 and 2200 h. Urine was collected over a 24 h period to determine the urinary GH level, which was expressed relative to the creatinine (Cr) levels. These measurements were performed before, 1, 2 and 4 weeks after the start of octreotide therapy. Serum GH (Dinabot, Tokyo:  $< 5 \text{ ng/ml}$ ), serum IGF-1 (Ciba-Corning, Tokyo: 100–383  $\text{ng/ml}$ ) and serum free thyroxine (free T4; Amerlex-MAB Free T4, Ortho-Clinical Diagnostics, UK: 1.0–1.8  $\text{ng/dl}$ ) were assayed with commercially available RIA kits. Urinary GH was assayed by EIA (Sumitomo Pharm. Osaka: 1.7–9.5  $\text{ng/g Cr}$ ).

Octreotide was administered subcutaneously with a portable continuous infusion pump (SP-3HQ, NIPRO, Osaka). Our practical regimen was designed with the purpose of reducing the daily dose and duration of treatment compared with the previous studies on continuous infusion [16–18]. Octreotide was infused at a dose of 5  $\mu\text{g}/\text{h}$  in 6 patients (daily dose, 120  $\mu\text{g}$ ) or 10  $\mu\text{g}/\text{h}$  in three patients (daily dose, 240  $\mu\text{g}$ ). The duration of preoperative treatment was two weeks in two patients (cases 7 and 8), and 4 weeks in the other 7 patients.

Pituitary MRI (1.5 Tesla, Advantage, GE) was performed with T1-weighted SE sequences, 4 mm slices in sagittal and coronal sections which were vertical to their hard palates, native and with Gadopentetate Meglamine (1  $\text{mmol/kg}$ )

**Table 1.** Clinical characteristics of patients

Case no.	Age (yr) /sex	Tumor volume ( $\text{mm}^3$ )	Tumor extension	Octreotide dose ( $\mu\text{g}/24 \text{ h}$ )	Therapy duration (weeks)
1	53/F	1,820	suprasellar	240	4
2	55/F	1,150	intrasellar	240	4
3	36/M	1,670	intrasellar	120	4
4	46/M	1,260	intrasellar	120	4
5	32/M	2,360	intrasellar	120	4
6	46/M	290	intrasellar	120	4
7	35/M	640	intrasellar	120	2
8	53/F	550	intrasellar	120	2
9	32/F	16,700	suprasellar rt-cavernous	240	4

enhancement under as similar conditions as possible. MRI was performed before octreotide therapy in all patients, 1 and 2 weeks in three patients (cases 5, 7 and 8) and 4 weeks in seven patients (cases 1, 2, 3, 4, 5, 6 and 9) after commencement of the octreotide therapy. The tumor size was measured by tracing the tumor margin on each slice of MRI with a computerized digitizer (Aloka, Tokyo). A reduction rate more than 20% of the pretreatment size was considered significant [19]. Treatment with octreotide was terminated at the time of transsphenoidal surgery. In case 9, two separate operations were performed because the tumor was a macroadenoma with an extensive suprasellar expansion. All operations were performed by the same neurosurgeon. From one to three months after surgery, GH secretion patterns were assessed with reference to basal measurements of serum GH and the response to oral glucose load.

## Results

### Preoperative hormone levels

The serum and urinary GH concentrations were high preoperatively in all 9 patients, ranging from 7.4 to 83.0 ng/ml (mean  $\pm$  SD, 26.0  $\pm$  22.9 ng/ml) and from 37.6 to 651.5 ng/g Cr (mean  $\pm$  SD, 186.1  $\pm$  246.1 ng/g Cr), respectively. Octreotide treatment for 2 or 4 weeks resulted in suppression of serum and urinary GH concentrations in 8 out of 9 patients, to 0.8–12.0 ng/ml (mean  $\pm$  SD, 3.9  $\pm$  3.5 ng/ml) and to 1.8–94.6 ng/g Cr (mean  $\pm$  SD, 17.4  $\pm$  31.6 ng/g Cr), respectively (Fig. 1A). Serum IGF-1 concentrations were also initially high, ranging from 400.8 to 1544.5 ng/ml (mean  $\pm$  SD, 918.6  $\pm$  400.7 ng/ml) but decreased after octreotide therapy in 8 out of 9 patients to 181.2–697.2 ng/ml (mean  $\pm$  SD, 332.9  $\pm$  176.2 ng/ml). Octreotide therapy failed to reduce hormone levels in only one patient (case 9) who had an extensive suprasellar expansion and cavernous sinus invasion.

### Pituitary tumor size

Three patients had microadenoma (diameter < 1,000 mm<sup>3</sup>) and 6 patients had macroadenoma (diameter > 1,000 mm<sup>3</sup>). Two patients had suprasellar tumors (cases 1 and 9), and invasion

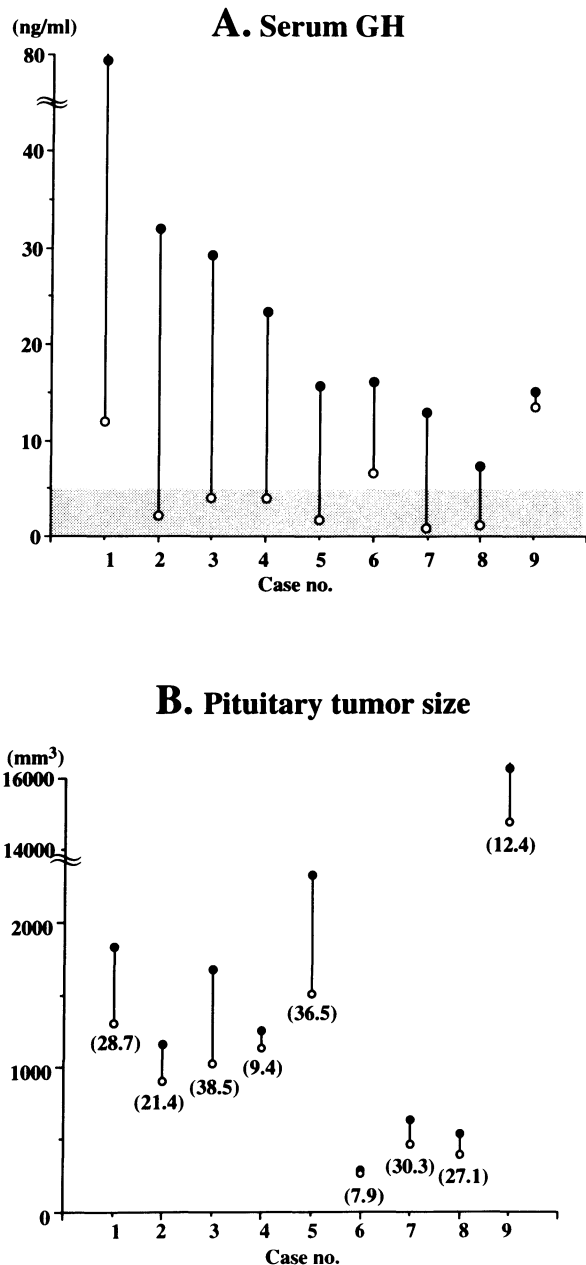


Fig. 1. A: Serum GH and B: pituitary tumor size in nine patients with acromegaly before (closed circles) and 2 or 4 weeks after commencement of octreotide therapy (open circles). The rates of reduction in tumor size (%) are given in parenthesis. The patients are arranged in the order shown in Table 1.

into the cavernous sinus was also present in one of them (case 9). The tumor size measured preoperatively before octreotide therapy did not correlate with indexes of GH hypersecretion.

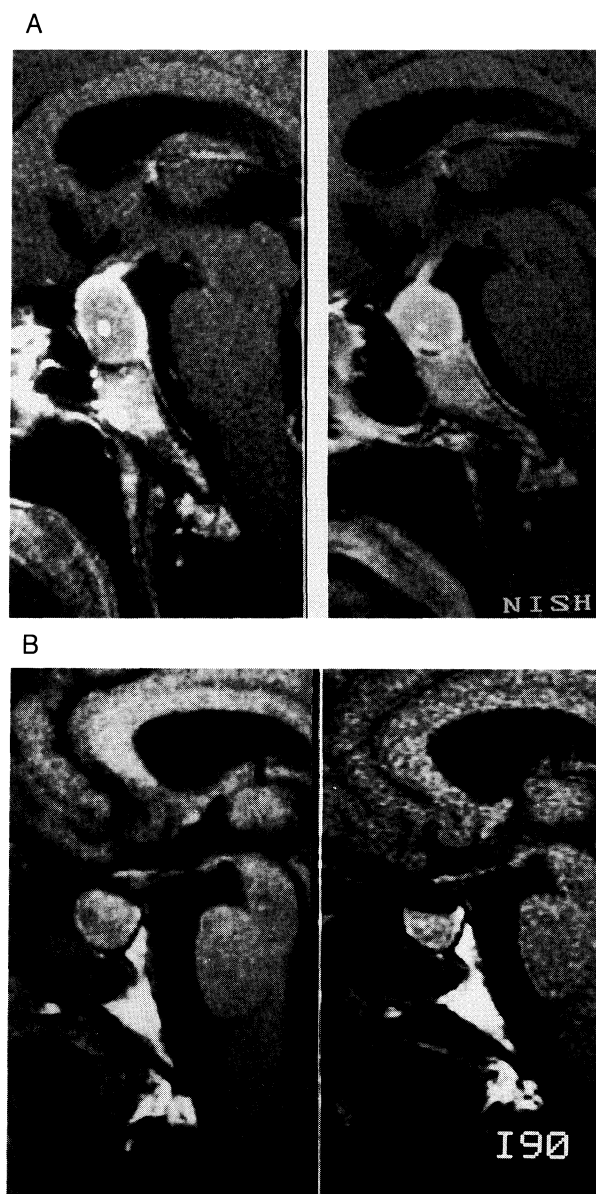


Fig. 2. Sagittal sections of MRI before (left) and 4 weeks after (right) commencement of octreotide therapy (A, case 1; B, case 5).

Octreotide therapy reduced pituitary tumor size, although the effects varied from one patient to another (range of reduction in tumor size, 7.9 to 38.5%). In particular, a considerable reduction in tumor size (> 20%) occurred in 6 of 9 patients (Fig. 1B). Fig. 2 shows the considerable effects on tumor reduction in two patients (cases 1 and 5). In one patient (case 1; Fig. 2A), the suprasellar expansion dramatically disappeared after octreotide therapy.

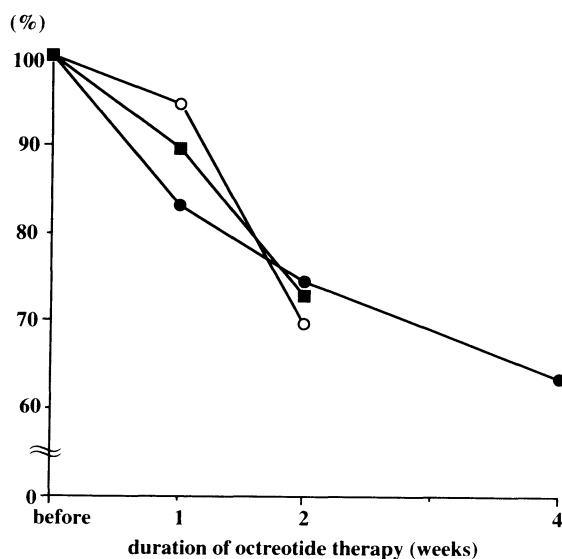


Fig. 3. Serial changes in pituitary tumor size in cases 5 (closed circles), 7 (open circles), and 8 (squares). They are expressed as a percentage of the initial tumor volume.

The time course of tumor volume in three patients on 120  $\mu\text{g/day}$  of octreotide is shown in Fig. 3, expressed as a percentage of the initial tumor volume. Tumor shrinkage was noted within the first week of therapy and continued during two or four weeks. In all three cases considerable tumor shrinkage (>20%) was seen within the first two weeks. The degree of tumor shrinkage did not correlate with that of GH suppression (Fig. 1A, B).

#### Side effects

In one patient (case 4), octreotide therapy reduced serum free T4 to 0.7 ng/dl, necessitating L-thyroxine replacement. After the operation, the level returned to normal and L-thyroxine replacement was discontinued.

#### Postoperative hormone levels

Postoperative GH secretion, referring to basal concentrations of serum GH and the response to glucose load, returned to normal levels in 8 of 9 patients within one to three months after surgery. In case 9, serum GH concentrations measured postoperatively were less than those measured preoperatively, but not normalized. Treatment with bromocriptine was performed in this case.

## Discussion

The major finding of our study was the preoperative tumor shrinkages with a small dose of octreotide, administered with a subcutaneous continuously infusion pump over a short period of 2 to 4 weeks.

Octreotide is known to suppress serum GH and shrink GH-producing tumors in acromegalic patients [5–7], since such pituitary adenomas usually contain a high density of somatostatin receptors with a high affinity for octreotide [20]. Continuous infusion of octreotide showed a better control of GH hypersecretion compared with intermittent injections in previous reports [14, 15]. In the present study, serum GH, IGF-1 and urinary GH concentrations were also significantly suppressed in 8 out of 9 patients with both 120 and 240  $\mu\text{g}/\text{day}$  of octreotide administered for 2 or 4 weeks. Only one patient (case 9) failed to respond, showing persistent GH hypersecretion during octreotide therapy. A deficiency of active adenylyl cyclase, which is less sensitive to octreotide [21], may explain the resistance to octreotide in this patient.

We also demonstrated considerable preoperative tumor shrinkage in 6 out of 9 patients. A few previous studies on continuous infusion with a variety of daily doses and periods [16–18] have not investigated the shrinkage of pituitary tumor with a small dose for a short duration as in our study. As in a previous report that octreotide induces a shrinkage of the tumor in approximately 50% of GH-producing tumors [6, 7], a beneficial result was obtained in tumor shrinkage although we used small doses for a short duration with a continuous infusion pump. Serial analysis of tumor size in three patients showed that tumor shrinkage was evident after the first week of therapy, and considerable tumor shrinkage was seen within the first two weeks even when the dose was as little as 120  $\mu\text{g}/\text{day}$ , indicating that octreotide therapy with a continuous infusion pump may be more cost- and time-effective than intermittent injections. In addition, the degree of tumor shrinkage two weeks after the start of octreotide therapy may become a reference for estimating whether octreotide will be effective as preoperative therapy, even though the number of subjects analyzed was limited.

In our study, eight patients without local invasion

were cured after surgery as confirmed by repeated examinations of hormonal profiles. Since subjects with intrasellar tumors are known to have a satisfactory prognosis after surgery, we could not conclude that octreotide therapy in this study improved the surgical result. In general, it is thought that a transsphenoidal surgery, without following octreotide therapy, can be sufficient to manage intrasellar microadenomas without local invasion. Nevertheless, a number of studies have also demonstrated the usefulness of preoperative octreotide treatment in shrinking pituitary tumors associated with subsequent improvement in the surgical remission rate in acromegalic patients with macroadenomas [9–11]. In addition, previous studies have shown that the surgical outcome in patients with microadenomas is better than in patients with macroadenomas [22]. Of particular interest was the outcome of treatment in case 1 in the present study; suprasellar expansion of the pituitary tumor disappeared after preoperative octreotide therapy. Octreotide can therefore be potentially sufficient as an adjunct therapy to subsequent transsphenoidal surgery for expansive macroadenomas.

Barkan *et al.* [8] also demonstrated substantial improvement in surgical outcome after preoperative treatment with intermittent injections of octreotide in patients with invasive macroadenomas, but in our study, one patient (case 9) with cavernous sinus invasion failed to be completely cured by surgery. Although the sample number is too small to draw a definite conclusion, a surgical cure would be difficult to achieve in patients with invasive tumors when only treated preoperatively with continuous octreotide in small daily doses over a short period, as our regimen. In fact the optimal dose and duration of continuous infusions remain undetermined particularly with regard to the maximal effect on tumor size [16–18], although Barkan *et al.* [8] suggested that octreotide therapy with intermittent injections seems to result in maximal effects within 8–12 weeks. Further control studies are required to establish the daily dose and duration of treatment with octreotide necessary to produce a satisfactory outcome [11, 23].

Long-term treatment with octreotide may be associated with increased likelihood of development of adverse effects, notably gallstone formation [24]. Continuous infusion octreotide therapy may reduce the rate of complications more

than intermittent injections. Only one patient in the present series developed reversible mild hypothyroidism but no major adverse effects were noted.

In conclusion, our study demonstrated that short-

term continuous subcutaneous infusion of a small dose of octreotide results in not only inhibition of GH hypersecretion but also shrinkage of tumor size prior to surgery in patients with GH-secreting pituitary adenomas.

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