Octreotide, but not bromocriptine, increases circulating insulin-like growth factor binding protein 1 levels in acromegaly

Wouter W de Herder, Piet Uitterlinden, Aart-Jan van der Lely, Leo J Holland and Steven WJ Lamberts

Department of Internal Medicine III, Erasmus University, Rotterdam, The Netherlands


Twenty-three patients with active acromegaly underwent serum sampling for growth hormone (GH), insulin and insulin-like growth factor binding protein 1 (IGFBP-1) after placebo or single doses of octreotide or bromocriptine. Integrated 24-h serum GH levels decreased by 90% after octreotide and 49% after bromocriptine. A statistically significant correlation between the course of GH levels after octreotide and bromocriptine was observed (p < 0.001). Octreotide, but not bromocriptine, induced a significant increase in integrated 24-h serum IGFBP-1 levels to 37.4 times the baseline values. Bromocriptine caused a non-significant increase in integrated 24-h serum IGFBP-1 levels, which argues against a direct regulatory effect of GH on IGFBP-1 production in acromegaly. In conclusion, octreotide induces in acromegaly the production of IGFBP-1, which occurs independently of the number of somatostatin receptors on the GH-secreting pituitary adenoma. The supposed inhibitory effect of IGFBP-1 on the biological effect of IGF-I might result in an additional clinical benefit in acromegalic patients as compared to treatment directed at the pituitary level.

WW de Herder, Department of Internal Medicine III and Clinical Endocrinology, University Hospital Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Acromegaly is a chronic state of growth hormone (GH) excess, usually due to a GH-secreting pituitary tumor. Insulin-like growth factor I (IGF-I) mediates many of the effects of GH (1), and has anabolic actions as well as hypoglycemic effects like insulin (2). Hepatic IGF-I production is regulated by GH (1). Unlike GH levels, IGF-I levels vary little throughout the day (1). The serum IGF-I level is a reliable parameter of excessive GH secretion in active acromegaly (3, 4).

In the circulation, more than 90% of plasma IGF-I is complexed to specific binding proteins (IGFBPs) (5), which modify the biological activity of IGF-I. The 28-kD IGFBP-1 is generally found to be an inhibitor of IGF-I actions, although some stimulatory effects of IGFBP-1 have been described (6). In vitro, IGFBP-1 secretion has been shown to be regulated primarily by insulin (6). Fasting levels of insulin and IGFBP-1 are correlated inversely in children and young adults (7). However, in aged individuals this correlation seems to disappear (7). Furthermore, IGF-I levels decrease with age, reflecting a diminished GH secretion (8-10). Previous studies have shown either normal or lowered IGFBP-1 levels in patients with active acromegaly as compared to healthy controls (8, 11-13).

In the case of persistently increased GH levels following neurosurgery for GH-producing pituitary tumors, adjunctive medical therapy is necessary. The dopamine agonists bromocriptine and quinagolide and the cyclic somatostatin analogs octreotide and lanreotide have been used to attenuate effectively both GH and IGF-I excess in acromegaly (14-19).

In cultured hepatoma (hep G2) cells, octreotide induces IGFBP-1 production. This stimulation seems to occur independent of GH and insulin concentrations (20).

In a number of different clinical settings several investigators have shown that the administration of native somatostatin 14 (SS-14), octreotide or lanreotide to healthy young subjects, GH-deficient subjects and acromegalics was followed by an increase in circulating IGFBP-1 levels (12, 13, 21-24). In a few studies an inverse correlation between circulating IGFBP-1 and insulin levels was found (12, 21), while in most studies no correlation could be demonstrated between IGFBP-1 and GH levels.

It has been suggested that IGFBP-1 may be another useful marker in evaluating the response of acromegaly to octreotide treatment in patients who experience clinical benefit but equivocal GH and IGF-I attenuation (11).

In order to characterize further the regulation of IGFBP-1 levels by octreotide in acromegaly, we compared the effects of a single dose of octreotide and bromocriptine on circulating IGFBP-1 levels in nonfasted acromegalic patients.
Subjects and methods

Subjects

Twenty-three consecutive, previously untreated patients with active acromegaly were included in the study: 11 females (age 37–77, mean 54 years) and 12 males (age 29–73, mean 51 years). The diagnosis was suspected by the presence of classical acromegalic features, and established by the presence of increased IGF-I levels (minimal 68 nmol/l, maximal 206 nmol/l, mean 125 nmol/l; normal values <43 nmol/l) (see Table 1). The sellar region was investigated by computed axial tomographic scan or T1-weighted magnetic resonance images in the coronal and sagittal planes, and a pituitary tumor was demonstrated in all patients.

Procedures

All patients underwent two experimental trials on two consecutive days.

From 08.00 h serum was sampled for GH, insulin and IGFBP-1 from an indwelling venous catheter at hourly intervals up to 18.00 h, followed by 2-h sampling to 06.00 h and a final sample taken at 07.00 h. Meals were taken at 08.30, 12.30 and 18.00 h. Serum glucose was sampled at hourly intervals from 08.00 h to 12.00 h. On day 1 a placebo (0.5 ml of 0.9% NaCl) was injected at 08.15 h. On the second day, the same protocol was repeated and 0.050 mg of octreotide acetate (Sandostatin®, Sandoz, Basle, Switzerland) was administered subcutaneously at 08.15 h. On the third day, 2.5 mg of bromocriptine (Parlodel®, Sandoz, Basle, Switzerland) was given orally at 08.00 h. The sampling protocol was discontinued at 20.00 h, however.

Immunoassays

Serum GH levels were determined by commercially available immunoradiometric assay (IRMA) supplied by Euro-Diagnostica, Apeldoorn, The Netherlands (intra-assay CV = 2.8%; interassay CV = 4.0%). Insulin levels were determined by IRMA obtained from Medigenix Diagnostics, Fleurus, Belgium (intra-assay CV = 4.5%; interassay CV = 12.2%). Total serum IGF-I was determined by radioimmunoassay (RIA), using kits obtained from Medigenix Diagnostics (intra-assay CV = 6.1%; interassay CV = 9.9%). Serum IGFBP-1 levels were determined by IRMA supplied by Diagnostic System Laboratories, Webster, Texas, USA (intra-assay CV = 6.0%; interassay CV = 3.5%). All samples were measured together in duplicate.

Statistics

Growth hormone, IGFBP-1 and insulin levels were also analyzed as area under the curve (AUC) values. Results are given as means ± SEM. Correlations were made by the Pearson two-tailed bivariate correlation test.

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Table 1. Patient data and biochemical parameters.

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<tr>
<th>Patient</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Basal fasting GH (µg/l)</th>
<th>Basal fasting glucose (mmol/l)</th>
<th>Basal fasting insulin (mU/l)</th>
<th>IGF-I (µg/l)</th>
<th>Basal fasting IGFBP-1 (µg/l)</th>
<th>Maximal IGFBP-1 increase after octreotide (times basal value)</th>
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a IGFBP-1: insulin-like growth factor binding protein 1.
Differences between the results at different times for the control, octreotide and bromocriptine administration days were calculated using the Wilcoxon matched-pairs signed rank test as a non-parametric test. All statistical analyses were performed using the commercial statistical software program SPSS for Windows, release 6.0 (SPSS Inc. USA). Statistical significance was defined as p < 0.05.

Results
No serious adverse effects were registered during the study. In Table 1, the individual fasting GH, glucose, insulin, IGF-I and IGFBP-1 levels are shown for the 23 untreated acromegalic patients. The relative increase in IGFBP-1 after octreotide is also shown in Table 1. This response shows a wide variation amongst the patients. No statistical relations were found between age, sex, fasting GH, glucose, insulin and IGF-I levels. Also, these parameters did not correlate with the degree of octreotide-induced increase in IGFBP-1 levels.

In Fig. 1, the mean GH, IGFBP-1 and insulin profiles are shown (mean ± SEM). After the acute sc administration of octreotide, a sharp increase in IGFBP-1 levels was observed. Maximal IGFBP-1 stimulation by octreotide was found 3 h after injection, whereafter a decline to control levels was observed after 7 h. The AUC for IGFBP-1 levels after octreotide increased to 37.4 times the control values (confidence limits 14.8–59.9 times; p < 0.001 vs control). The acute po administration of bromocriptine resulted in a slight increase in IGFBP-1 levels (5.4 times increase of AUC; confidence limits 2.0–8.9 times). This increase was not significant statistically, however. Octreotide attenuated the post-breakfast insulin secretion but not the increase in insulin levels in response to lunch and dinner. There was no statistically significant correlation between the IGFBP-1 and insulin levels in the baseline study either after octreotide or after bromocriptine. After the acute sc administration of octreotide, GH levels reached a nadir after 4 h and suppression was sustained for 11 h. After bromocriptine, less suppression of GH levels was observed but the effect also remained for at least 11 h. The AUCs for GH after octreotide and bromocriptine decreased by 90% (confidence limits 88.5–92.3%) and 48.8% (confidence limits 34.1–63.5%), respectively. There was a significant correlation between the course of GH levels after octreotide and after bromocriptine (p < 0.001). There was no correlation between the GH and IGFBP-1 levels at baseline either after octreotide or after bromocriptine. This indicates that the increase in IGFBP-1 levels occurs independently of the somatostatin receptor status of the GH-secreting pituitary adenomas.

Discussion
As expected, both octreotide and bromocriptine lowered serum GH levels significantly in our acromegalic patients.
The observed close correlation between the responsiveness of GH to octreotide and bromocriptine is in agreement with previous observations in a larger number of untreated acromegalic patients by van der Lely et al. (25). Additionally, octreotide, but not bromocriptine, induced a significant increase in serum IGFBP-1 levels. Ezzat et al. have shown that after the acute administration of octreotide to fasted, normal young healthy, GH-deficient and acromegalic subjects a significant increase in serum IGFBP-1 levels occurs within 2–3 h following injection (13, 22). Wolthers et al. have reported similar results with the acute administration of lanreotide to normal healthy subjects (24). Both groups of investigators demonstrated that the somatostatin analog-induced increase in serum IGFBP-1 was not related to an initial preceding suppression of peripheral insulin levels (13, 22, 24). In contrast to these observations, however, Cotterill et al. demonstrated in healthy young subjects that infusion of octreotide caused a decrease in circulating insulin levels, which was subsequently followed by a rapid increase in IGFBP-1 levels (21). The serum glucose levels did not change during these studies. They concluded that their findings were consistent with an inverse effect between insulin and IGFBP-1 production, although they could not exclude a direct effect of octreotide on IGFBP-1 (21). Recently, Fredstorp et al. studied the effects of a 14-day treatment period in acromegalic patients in which octreotide was administered three times a day. They demonstrated a significant increase in mean 11-h (07:00–18.00 h) IGFBP-1 levels during treatment. A significant inverse correlation was found in this study between mean IGFBP-1 levels and the mean of three insulin measurements at 0, 1 and 2 h after the morning octreotide injection (12). In our studies, octreotide abolished the insulin increase induced by food intake and “simultaneously” caused an IGFBP-1 increase. However, we could not demonstrate a significant correlation between the course of circulating insulin and IGFBP-1 levels. Recently, Orskov et al. demonstrated that the somatostatin analog-induced increase in IGFBP-1 in young healthy volunteers could be abolished by hyperinsulinemia. They suggested that the intake of meals immediately after the injection of octreotide may induce hyperinsulinemia and thereby suppress the rise in IGFBP-1 levels (23). In our studies and those of Fredstorp et al. this effect does not occur in non-fasting acromegalic (12). Ezzat et al. reported that the stimulation of IGFBP-1 by octreotide in normal young healthy and GH-deficient subjects occurred independently of GH, while they suggested a GH-mediated IGFBP-1 regulation in acromegalis (13). In our studies, bromocriptine and octreotide both suppressed significantly the circulating GH levels. However, bromocriptine-induced GH suppression was not accompanied by a significant increase in IGFBP-1 levels. There was also no correlation between the course of GH and IGFBP-1 levels. These findings argue against a direct regulatory effect of GH on IGFBP-1 production in acromegaly. In cultured human hepatoma cells (hep G2), Ren et al. have found evidence for a direct induction of IGFBP-1 mRNA expression by octreotide, but this effect was first noted only after 12 h of co-incubation of the cells with octreotide (20).

As IGFBP-1 has, under certain conditions, IGF-I antagonistic actions, the octreotide-induced increase in IGFBP-1 may result in a decreased bioavailability of IGF-I. This might contribute to a decrease in disease activity, which is additional to that obtained by a decrease in GH and IGF-I levels. Therefore, this may give octreotide an additional therapeutic value as compared to other treatment modalities like bromocriptine, which are only directed at the pituitary level.

In conclusion, octreotide, but not bromocriptine, induces IGFBP-1 release in active acromegaly. The results obtained after the administration of bromocriptine argue against a direct GH effect on IGFBP-1 in acromegaly. Octreotide induces in acromegaly the production of IGFBP-1, which occurs independently of the number of somatostatin receptors on the GH-secreting pituitary adenoma. This might result in an additional clinical benefit in acromegalic patients as compared to treatment directed at the pituitary level, like surgery, radiotherapy and/or dopamine agonist therapy.

References

8. Juul A, Main K, Blum WF, Lindholm J, Ranke MB, Skakkaebaek NE. The ratio between serum levels of insulin-like growth factor (IGF-I) and the IGF binding proteins (IGFBP)-1, 2 and 3 decreases with age in healthy adults and is increased in acromegalic patients. Clin Endocrinol (Oxf) 1994;41:85–93

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