Octreotide Therapy of Pediatric Hypothalamic Obesity: A Double-Blind, Placebo-Controlled Trial

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Hypothalamic obesity is a devastating complication in children surviving brain tumors and/or cranial irradiation. These subjects are thought to exhibit autonomic dysregulation of the β-cell, with insulin hypersecretion in response to oral glucose tolerance testing (OGTT). We report the results of a randomized, double-blind, placebo-controlled trial of octreotide therapy for pediatric hypothalamic obesity. Eighteen subjects [weight, 100.6 ± 5.6 kg; body mass index (BMI), 37.1 ± 1.3 kg/m²] received octreotide (5–15 μg/kg/d sc) or placebo for 6 months.

With octreotide, a weight (mean ± SEM) was +1.6 ± 0.6 vs. +9.1 ± 1.7 kg for placebo (P < 0.001). ΔBMI was −0.2 ± 0.2 vs. +2.2 ± 0.5 kg/m², respectively (P < 0.001). OGTT documented Δinsulin response (peak − basal) of −417 ± 304 pm after octreotide vs. +216 ± 215 pm after placebo (P = 0.034). Improvement in physical activity by parent report was noted with octreotide, but not placebo (P = 0.03). For the octreotide group, changes in quality of life positively correlated with changes in insulin response (P = 0.041). Complications and adverse events were mild and self-limited.

These data demonstrate the beneficial effects of octreotide in pediatric hypothalamic obesity. Octreotide suppressed insulin, and stabilized weight and BMI. Improved quality of life correlated with the degree of insulin suppression. Octreotide was safe and well tolerated. (J Clin Endocrinol Metab 88: 2586–2592, 2003)

Abbreviations: ALL, Acute lymphoblastic leukemia; BMI, body mass index; HbA1c, hemoglobin A1c; HV, Height velocity; OGTT, oral glucose tolerance testing; QoL, quality of life; SJCRH, St. Jude Children’s Research Hospital; U.T., University of Tennessee; VMH, ventromedial hypothalamus.

Patients and Methods

This protocol was approved by the St. Jude Children’s Research Hospital (SJCRH) and the University of Tennessee (U.T.) Institutional Review Boards, the SJCRH Central Protocol Scientific Review and Monitoring Committee, the U.T. Clinical Research Center’s Scientific Advisory Council, and the LeBonheur Children’s Medical Center Pediatric...
Research Committee. Twenty subjects, age 8–18 yr, with intractable weight gain following therapy for tumors were recruited to take part in this study. Patients were included if: 1) they had been diagnosed with a brain tumor or had previously received cranial irradiation for ALL; 2) they survived greater than 1 yr post diagnosis without recurrence; 3) they demonstrated at least one other endocrinopathy, as a marker of hypothalamic damage; 4) their rate of normalized weight gain was greater than 2 sd above the mean for age (20); and 5) they were ambulatory. Patients were excluded if: 1) they had previously demonstrated voluntary weight loss; 2) they were receiving any medications for weight loss; 3) they exhibited diabetes mellitus (although impaired glucose tolerance was allowed); 4) they had documented cardiac dysfunction precluding normal exercise tolerance, as demonstrated by a shortening fraction of less than 0.12 on M-mode echocardiogram; 5) their GH status changed during the course of the study; 6) they were receiving supraphysiologic (>15 mg/m²d) hydrocortisone therapy; and 7) they had a history of hepatic or gallbladder disease.

Subjects were admitted to the U.T. Pediatric Clinical Research Center satellite at LeBonheur Children’s Medical Center at month 0 for physical examination, baseline laboratory studies including leptin, IGF-I, hemoglobin A₁c (HbA₁c), stool fat analysis, gallbladder ultrasound, and a 3-h oral glucose tolerance testing (OGTT) with simultaneous insulin levels. A 3-d food record was kept by the subject before the visit, which was reviewed in the presence of the dietician. QoL was assessed on child-report and parent-report of four aspects of QoL (cognitive, physical, psychological, social) using the Pediatric Cancer Quality of Life (PCQL-32, version 1.0 (21, 22). This instrument was administered to both the patient and the parent simultaneously, separately, and in a double-blind fashion.

Patients were randomized in a double-blind fashion to receive either octreotide or placebo sc for 6 months in an escalating dosage schedule, starting with injection volumes to deliver 5 μg/kg/d (divided into three daily doses), and with bimonthly increments of 5 μg/kg/d to a maximum dosage of 15 μg/kg/d (divided into three daily doses) by the beginning of month 5. Subjects visited their local pediatric endocrinologist bimonthly for physical examination, height and weight measurement, HbA₁c, and thyroid function testing. Injection volumes were increased at these bimonthly intervals based on the weight at that visit. At month 6, patients revisited SJCRH and the U.T. Pediatric Clinic Research Center for full reassessment, repeating all month 0 evaluations in a double-blind fashion. Each patient’s code was broken only after all evaluations were completed.

Statistical analysis

This study was designed as a prospective, randomized, double-blinded, placebo-controlled clinical trial. The sample size (10 on drug and 10 on placebo) was calculated for the primary hypothesis that increase of weight in 6 months by patients on octreotide is less than that by patients on placebo. The test of comparison is designed with a significance level of 0.05 and power of 0.8 for detecting a difference of 4.7 kg between the two groups. For the analysis, we used a two-sided t test in terms of the difference of changes (from months 0–6) between the two groups (octreotide and placebo) for comparing the changes in weight (Δweight) and BMI (ΔBMI) (23). Because the change of weight may be partially due to the change in height and due to the unequal ratios of males to females in the two groups, we performed these analyses using a mixed model (24, 25) with the covariates of height, gender, and treatment (octreotide and placebo), by which the effect of treatment was estimated and tested by separating from effects of height and gender.

Data are expressed as means ± SEM. Changes in IGF-I, leptin, HbA₁c, height velocity (HV), and caloric intake over the 6 months of study were analyzed using a repeated measurement model. Significance of changes in insulin secretion was assessed by: 1) fasting insulin concentrations using paired t test; 2) change in insulin response amplitude (peak insulin – fasting insulin) using paired t test and median test (the latter is more powerful when tail of distribution is heavy as that for these data); and c) overall pattern of the insulin response curve (ANOVA with repeated measures). Data related to the PCQL-32 were explored using a two-sided t test to test the changes in QoL (ΔQoL) over the 6 months of treatment (a negative value infers improvement). Lastly, ΔQoL was compared with changes in insulin measures by standard linear regression analysis.

Results

Demographics

Demographics are shown in Table 1. Twenty patients (11 male, 9 female), age 14.2 ± 0.7 yr, were recruited. Two subjects were recruited from the SJCRH Pediatric Endocrinology Clinic, and 18 others were referred from other institutions for participation. Thirteen subjects had craniopharyngioma, 4 subjects had hypothalamic astrocytoma, 1 had pineal germinoma, and 2 subjects had ALL and received 24 Gy of cranial irradiation at diagnosis. Of these, 18 were hypothyroid and receiving l-thyroxine, 15 were ACTH deficient and receiving hydrocortisone, 13 had diabetes insipidus and were receiving desmopressin, and 7 were receiving sex hormone supplementation. Of the 9 who had completed their growth, 7 had been previously tested and found to be GH deficient; of the 11 still growing, 10 had been tested and were found to be GH deficient. Eight subjects were receiving human GH therapy. Mean weight (±SEM) was 96.8 ± 5.7 kg, BMI was 36.3 ± 1.3 kg/m², and annualized weight gain before study initiation was 17.1 ± 3.0 kg/yr. Two subjects

| TABLE 1. Demographics of the hypothalamic obesity cohort, stratified by treatment group |
|---------------------------------|-----------------|-----------------|
| Age (yr)                        | Octreotide (n = 10) | Placebo (n = 10) |
| Sex                             | 13.8 ± 1.2       | 14.2 ± 0.9      |
| Diagnoses                       | 6 M, 4 F         | 5 M, 5 F        |
| Cranioopharyngioma, 6           | Hypothalamic astrocytoma, 2   | Hypothalamic astrocytoma, 1 Germinoma, 1 |
| ALL, 2                          | Optic pathway glioma, 1       | 7 Caucasians 2 African-Americans 1 Cuban-American |
| Race                            | 10 Caucasians    | 7 Caucasians    |
| Initial height (cm)             | 160.7 ± 3.9      | 163.2 ± 5.1     |
| Initial weight (kg)             | 95.4 ± 8.8       | 98.1 ± 7.7      |
| Initial BMI (kg/m²)             | 36.4 ± 2.4       | 36.2 ± 1.3      |
| Annualized weight gain (kg/yr)  | 15.0 ± 3.9       | 20.3 ± 4.5      |
| History of surgery              | 8                | 8                |
| History of cranial irradiation  | 10               | 10               |
| History of chemotherapy         | 2                | 2                |
| Receiving GH therapy            | 2                | 5                |

Data are expressed as mean ± SEM.
were discontinued from the study before the month 6 visit. One subject, randomized to octreotide, at month 2 exhibited a recurrence of her craniopharyngioma (retrospectively noted on her prerandomization magnetic resonance imaging), and another developed diabetic hyperosmolar nonketotic coma after 4 months of placebo treatment; their data are not included. Eighteen subjects completed the 6 months of study.

Body weight, BMI, caloric intake, leptin

The nine subjects treated with octreotide exhibited Δweight of +1.6 ± 0.6 kg (range −0.9 to +5.3), and ΔBMI of

-0.2 ± 0.2 kg/m² (range −0.7 to +0.9), whereas the nine subjects treated with placebo exhibited Δweight of +9.2 ± 1.7 kg (range +3.8 to +19.8; P < 0.001), and ΔBMI of +2.2 ± 0.5 kg/m² (range +0.1 to +4.4; P < 0.001), respectively. Bi-monthly weight and BMI changes are tabulated in Table 2. A somewhat more beneficial effect of octreotide was noted upon reaching the maximum dose of 15 µg/kg/d. Change in caloric intake between months 0 and 6 was −200 ± 103 vs. +103 ± 513 kcal/d (P = NS), and Δleptin was −12.4 ± 6.9 vs. −5.5 ± 4.6 ng/ml (P = NS) on octreotide vs. placebo, respectively.

Glucose and insulin

Glucose response curves to OGTT are exhibited in Fig. 1, A and B, and glucose dynamic parameters are listed in Table 3. The change in fasting glucose was increased with octreotide therapy (+0.85 ± 0.29 vs. +0.07 ± 0.28 mm; P = 0.076 for t test, 0.022 for median test). Although the change in glucose response to OGTT with octreotide therapy was higher than placebo (+0.45 ± 0.55 vs. −0.06 ± 0.21 mm), and the glucose excursion after octreotide therapy was increased, the difference was not significant in either analysis.

At month 0, both groups exhibited early and rapid insulin excursions to glucose challenge, and there was no significant difference in insulin excursion or dynamics between groups (Fig. 1, C and D). After octreotide treatment, the early insulin excursion was attenuated, while placebo-treated subjects did not exhibit a change in insulin secretion. Table 3 lists quan-

TABLE 2. Changes in weight and BMI between bimonthly measurements in patients with hypothalamic obesity treated with either octreotide or placebo

<table>
<thead>
<tr>
<th></th>
<th>Months 0–2</th>
<th>Months 2–4</th>
<th>Months 4–6</th>
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</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (n = 9)</td>
<td>+0.08 ± 0.54</td>
<td>+1.96 ± 1.36</td>
<td>−0.43 ± 0.87</td>
</tr>
<tr>
<td>Placebo (n = 9)</td>
<td>+3.60 ± 1.05</td>
<td>+2.44 ± 0.44</td>
<td>+3.08 ± 0.73</td>
</tr>
<tr>
<td>Difference (drug-placebo)</td>
<td>−3.52 ± 1.18</td>
<td>−0.48 ± 1.36</td>
<td>−3.50 ± 1.13</td>
</tr>
<tr>
<td>BMI change (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Octreotide (n = 9)</td>
<td>−0.8 ± 0.27</td>
<td>+0.59 ± 0.47</td>
<td>−0.64 ± 0.42</td>
</tr>
<tr>
<td>Placebo (n = 9)</td>
<td>+1.19 ± 0.31</td>
<td>+0.28 ± 0.19</td>
<td>+0.70 ± 0.28</td>
</tr>
<tr>
<td>Difference (drug-placebo)</td>
<td>−1.27 ± 0.41</td>
<td>+0.31 ± 0.49</td>
<td>−1.34 ± 0.49</td>
</tr>
</tbody>
</table>

Fig. 1. Excursions of glucose (A and B) and insulin (C and D) in response to OGTT both before (black squares) and after (white squares) 6 months of octreotide (A and C) or placebo (B and D) therapy in children with hypothalamic obesity. To convert glucose concentrations from mEq/l to mg/dl, multiply by 18; to convert insulin concentrations from µIU/ml, multiply by 0.1394.
titative changes in insulin dynamics with octreotide therapy. At month 0, fasting and peak insulin levels and insulin response (peak – fasting) were similar after treatment in both groups. At month 6, fasting insulin levels were similar and unchanged; however, peak levels to OGTT and insulin amplitude were diminished in subjects treated with octreotide. The change in insulin amplitude was $-0.11 \pm 0.04$ in the child group and $-0.33 \pm 0.05$ in the parent group. These changes were not statistically significant. ANOVA with repeated measures demonstrated a significant decline in insulin excursion with octreotide ($P < 0.001$).

**QoL**

No significant changes were noted on any measure for child-reported ΔQoL. However, in the parent report, significant improvements in ΔQoL were noted in the octreotide group for physical ($P = 0.05$), psychological ($P = 0.03$), and social ($P = 0.04$) functioning. Upon comparison of the ΔQoL between octreotide and placebo groups, there was a significant improvement in physical functioning based on the parent report ($P = 0.03$). There were no significant differences detected for other QoL measures.

Linear regression analysis between Δinsulin response and ΔQoL revealed a significant positive correlation with octreotide therapy compared with placebo ($r = +0.65$, $P = 0.041$). Changes in other measures did not correlate with either ΔQoL or Δinsulin response.

**HV, IGF-I**

Octreotide suppresses GH secretion and IGF-I levels (26). Although the subjects in our study were GH deficient due to their tumors or therapy, some had completed their growth ($n = 9$), whereas others were receiving GH therapy ($n = 3$). The effects of octreotide on HV in those still growing ($n = 9$), and IGF-I were assessed. Those on placebo and no GH ($n = 2$) had a HV of $3.3 \pm 0.3$ cm/6 months, whereas those on octreotide and no GH ($n = 4$) had a HV of $1.9 \pm 0.2$ cm/6 months. However, during the 6-month open-label follow-up of this subgroup, their HV improved to $2.8 \pm 0.3$ cm/6 months while still receiving octreotide. Of those receiving GH therapy, those on placebo ($n = 2$) had a HV of $5.1 \pm 1.0$ cm/6 months, whereas the one subject receiving octreotide had a HV of $3.7 \pm 0.6$ cm/6 months. IGF-I levels were essentially unchanged with octreotide. Those receiving octreotide plus GH ($n = 3$) exhibited a ΔIGF-I of $+164 \pm 93$ ng/ml, those receiving octreotide without GH ($n = 6$) had a ΔIGF-I of $-22 \pm 17$, those on placebo plus GH ($n = 2$) had a ΔIGF-I of $-37 \pm 240$, and those on placebo without GH ($n = 7$) had a ΔIGF-I of $-24 \pm 22$ ng/ml ($P = \text{NS}$).

**Safety**

All nine subjects receiving octreotide noted abdominal discomfort and diarrhea, which resolved by the second month of therapy. Three placebo-treated subjects also complained of diarrhea. All subjects had measurements of fecal fat performed at month 0 and month 6. In each instance, measurements were negative, arguing against the possibility of fat malabsorption due to octreotide therapy. Of the nine subjects who received octreotide, four exhibited either cholesterol gallstone or sludge formation upon gallbladder ultrasound at month 6. These four were treated during the 6-month open-label extension period with ursodiol 300 mg
orally twice daily, and despite remaining on therapy, their gallbladder anomalies resolved upon the subsequent 12-month ultrasound. Although two subjects receiving octreotide developed mild glucose intolerance at month 6, none of the nine subjects developed overt diabetes mellitus. However, one African-American subject with acanthosis nigricans, originally assigned to the placebo group, and who exhibited impaired glucose tolerance at both month 0 and month 6, developed diabetes during the open-label extension, and octreotide was discontinued. HbA1c levels increased from 5.4 ± 0.1 to 5.8 ± 0.1% with octreotide treatment, and from 5.6 ± 0.1% to 5.7 ± 0.1% with placebo. All others with normal glucose tolerance at baseline maintained normal glucose tolerance, even after 1 yr of therapy.

Discussion

Hypothalamic damage is a frequent sequel of cranial insult, due to head trauma, posterior fossa brain tumors, surgery, or radiation (2, 4, 27). The most common manifestations of such damage are the various components of hypopituitarism, i.e., GH deficiency, central hypothyroidism, adrenal insufficiency, hypopagondism or precocious puberty, and diabetes insipidus. In addition, obesity has been associated with cranial insult. Recently, we reported a direct relationship between hypothalamic damage and the rate of BMI increase and development of obesity in survivors of childhood brain tumors (28). This phenomenon, termed “hypothalamic obesity,” is unresponsive to diet, exercise, and most pharmacologic manipulations.

The VMH is the site of afferent hormonal negative feedback on the control of energy balance. Insulin from the pancreas, leptin from adipose tissue, ghrelin from the stomach, and pancreatic polypeptide 3–36 from the small intestine, each bind to their individual receptors in the VMH (29–32) to provide peripheral hormonal information on energy intake and utilization. Damage to the VMH results in the inability to transduce these peripheral signals, with resultant excessive caloric intake and decreased energy expenditure, leading to incessant energy storage and intractable obesity.

Rodent studies suggest that VMH lesions promote insulin hypersecretion, which can be obviated by pancreatic vagotomy (33–35). The vagus promotes increased β-cell activity through three separate mechanisms (36, 37). First, acetylcholine binds to the M3 muscarinic receptor on the β-cell, opening a sodium channel, which augments depolarization (38), and leads to a widening of the voltage-gated calcium channel, and insulin vesicular exocytosis (33, 39, 40). Second, acetylcholine increases phosphorylase activity within the β-cell, which increases conversion of phosphorylidyinositol to diacylglycerol and inositol triphosphate (36, 41–43), both of which increase vesicle exocytosis. Third, the vagus stimulates the release of glucagon-like peptide-1 from intestinal L-cells, which binds to the glucagon-like peptide-1 receptor on the β-cell and induces adenyl cyclase, with conversion of intracellular ATP to cAMP. Protein kinase A is activated, which promotes phosphorylation of vesicular proteins, which further increase insulin exocytosis (44, 45). Octreotide, by binding to the somatostatin receptor-5 on the β-cell membrane, limits the opening of the voltage-dependent calcium channel, and attenuates the early response of insulin to a glucose challenge (26, 46).

Subjects with hypothalamic obesity exhibit insulin hypersecretion, particularly during the early phase of the OGTT (1). We postulated that octreotide suppression of early insulin secretion would attenuate the weight gain (19). In the current study, octreotide treatment resulted in a stabilization of weight and BMI, whereas placebo treatment resulted in no change in the rate of weight or BMI gain. Our results are not as robust as in our earlier pilot study, perhaps because the octreotide dosage was escalated more slowly, and did not reach its maximum until the end of the fourth month. Indeed, the majority of the weight loss in the drug-treated group occurred between months 4 and 6. The early insulin response was clearly attenuated with drug treatment (Fig. 1C). Furthermore, the decline in insulin response correlated with improvement in QoL. Patients with hypothalamic obesity routinely have malaise and lethargy, along with decreased physical activity and psychological well being. This has previously been ascribed to the psychological trauma that such brain tumor survivors experience, due to the cranial radiation that some patients receive, or due to the development of the obesity itself. Our data suggest, but do not prove, that a hormonal aberration may contribute to the altered QoL in these patients. Furthermore, they suggest that correction of this pathophysiological state, even for a brief duration, may lead to clinically meaningful improvement.

We cannot completely rule out other potential mechanisms of octreotide action in the this study, such as: modulation of other gastrointestinal hormones (45); slowing of gastric emptying and gastrointestinal motility, with nutrient malabsorption (47); direct effects on appetite (48, 49); or direct effects on the adipocyte (50, 51). However, these mechanisms seem less likely. If a mechanism other than insulin suppression was responsible for the weight loss, nonobese subjects receiving octreotide for acromegaly or other disorder would be expected to lose weight and fat mass; indeed long-term octreotide usage has minimal effect on these parameters (52). A last possible other mechanism is suppression of gastric ghrelin secretion (53); This also seems less likely, as subjects with hypothalamic obesity have VMH damage, which would prevent ghrelin’s stimulation of neuropeptide Y to promote feeding (31); however, this awaits scientific confirmation.

Octreotide therapy was well tolerated in this cohort. Despite the regimen of three injections per day, compliance was deemed to be excellent in all but one subject. The initial gastrointestinal distress and diarrhea was self-limited, and fat malabsorption was not seen. Four subjects required an increase in their L-thyroxine dosage to maintain their free T4 at its pretreatment level. The occurrence of cholesterol gallstones with octreotide therapy, while well documented in adults (26), was easily reversed with ursodiol therapy (54). The rise in fasting glucose and increased glycemia was not clinically significant or deleterious to overall glucose tolerance.

This study suggests that insulin hypersecretion may be responsible both for weight gain and feelings of malaise in subjects with hypothalamic obesity. We recently noted decreased BMI and changes in macronutrient preference in a
subgroup of obese adults who exhibited insulin hypersecretion during the early phase of the OGTT but without cranial pathology (55). The similarities of effect in these two disparate cohorts suggest that insulin suppression therapy using octreotide may be a safe and effective therapeutic modality in patients with obesity due to insulin hypersecretion, of which cranial insult is a subset.

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