FINAL HEIGHT IN GIRLS WITH CENTRAL IDIOPATHIC PRECOCIOUS PUBERTY TREATED WITH GnRH ANALOGUE AND OXANDROLONE

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ABSTRACT

Context: Gonadotropin-releasing hormone analogues (GnRHa) are considered the treatment of choice for central precocious puberty (CPP). During GnRHa administration, the suppression of the pituitary-gonadal axis results in decreased rates of linear growth and skeletal maturation, and in improved adult height. However, in some patients the growth deceleration is so marked that the expected improvement in predicted adult height is not achieved.

Objective: The objective of this study was to assess whether the addition of oxandrolone (Ox) may affect the height outcome of patients with CPP and growth deceleration during GnRHa treatment.

Design: This was an open-label, clinical study.

Setting: The study was performed at a Pediatric Endocrinology referral clinic.

Patients: Twenty patients with CPP and marked growth deceleration during GnRHa treatment, were studied.

Interventions: Treatment consisted of GnRHa (Leuprolrelina, 3.75 mg i.m. every 28 days) alone (10 patients) or in combination with Ox (0.06 mg/kg/day p.o.) (10 patients).

Main Outcome Measure: The main outcome measure is the patients’ adult height.

Results: The adult height of the patients treated with GnRHa plus Ox was significantly higher than pre-treatment predicted adult height (PAH) (162.6 ± 2.3 vs 154.8 ± 1.7 cm, mean ± SEM, p<0.05), and target height (162.6 ± 2.3 vs 158.0 ± 1.9, p>0.05) (TH). Patients treated with GnRHa alone reached an adult height similar to the pre-treatment PAH (151.9 ± 1.2 vs 155.4 ± 2.1 cm) but significantly lower than TH (151.9 ± 1.2 vs 156.6 ± 1.4 cm, p<0.005). No side effects were recorded in either group of patients.

Conclusions: combined GnRHa and Ox therapy is a viable treatment option for children with CPP and marked growth deceleration during treatment with GnRHa alone.
INTRODUCTION

Central precocious puberty (CPP) is defined as the onset of sexual development before the age of 8 yrs in girls and 9 in boys. The precocious activation of the hypothalamic-pituitary-gonadal axis results in an early rise in gonadal steroids, which, in turn, is responsible for the accelerated linear growth and bone maturation that leads to impaired final height (1, 2). GnRH analogues (GnRHa) are the treatment of choice in CPP (3). The aims of such therapy are to block pubertal maturation and prevent early menarche as well as to slow bone maturation and improve adult height. In most cases, treatment with GnRHa effectively halts pubertal development and improves final height (4, 5). However, in some patients, treatment does not just normalize height velocity but induces an inappropriate deceleration of the growth rate with ensuing impaired final heights (4-7). Recent studies showed that in such a subset of patients the addition of GH to the GnRHa therapy results in increased final height as compared with that of patients treated with GnRHa alone (6, 8).

Oxandrolone (Ox), a nonaromatizable androgen which has a high anabolic to androgenic ratio compared to testosterone (9, 10), has been used to stimulate growth in boys with constitutional delay of growth and puberty (11-13). The exact mechanism of its growth-promoting effect has not been completely elucidated. An activating effect of Ox on the somatotropic axis via distinct neuroendocrine secretory mechanisms was reported by some authors (14, 15) but not confirmed by others (16, 17). In addition, IGF-1 concentrations were unaffected by Ox administration (11), further supporting a somatotrophic-independent mechanism of action of the steroid. Since androgen receptors are expressed in the growth plate from the developing bone (18), and androgens regulate
both proliferation and differentiation of cultured epiphyseal chondrocytes (19-23), a direct
effect on the growth plate may explain the growth promoting action of Ox.

This study was designed to assess whether Ox may affect the height outcome in
patients with CPP and growth deceleration during GnRHa treatment. Ten girls with
idiopathic CPP and severe growth deceleration during GnRHa treatment were treated with
combined therapy. Their data were compared with those of 10 idiopathic CPP girls
matched for auxological data, duration of treatment, and growth deceleration, treated with
GnRHa alone.

SUBJECTS AND METHODS

Subjects

This study was approved by the Clinical Research Committee of the Department of
Pediatrics at the University of Parma (Parma, Italy), and informed consent was obtained
from the children and their parents. Ten girls with idiopathic CPP, whose height velocity
during GnRHa treatment (Leuprolelina, 3.75 mg i.m. every 28 days) decreased below the
25th centile for chronologic age, received 0.06 mg/kg/day of Ox p.o. for 1.7 ± 0.15 (mean ±
SEM) yrs (Group 1). The diagnosis of idiopathic CPP was based on the gonadotropin
response to the GnRH stimulation test and normal MRI of the central nervous system. The
auxologic features of the patients before and during treatment are reported in Table 1.
Height velocity deceleration was recorded after 2.8 ± 0.3 yrs of GnRHa treatment and at
that time Ox was added to the treatment schedule. The Ox dose was selected based on
the data on Ox treatment in Turner’s syndrome (24).

Data from 10 girls with idiopathic CPP (Group 2) matched for chronologic age, bone
age, duration of GnRHa treatment (5.0 ± 0.3 yrs), and growth deceleration during GnRHa
therapy, were compared with those of Group 1 to evaluate the effect of Ox
supplementation on final height. Their auxologic data are reported in Table 2.
All patients were euthyroid, had normal IGF-1 plasma concentrations, and were evaluated at the start of treatment and every 6 months thereafter. Bone age was determined by the method of Greulich and Pyle (25) by the same observer, and adult height was predicted according to the Bayley and Pinneau method (26). Pubertal staging was evaluated using the method of Tanner (27). Gonadotropin concentrations were measured every 12 months before, and 15, 30, 60, 90, and 120 min after the iv administration of 100 µg of GnRH. To assess suppression of the pituitary-gonadal axis during treatment, the GnRH stimulation test was performed on day 25 after the last injection of GnRHa. Target height (TH) was calculated from the mean height of the parents, adjusted for sex, as described by Tanner et al. (28). Adult height was considered to be attained when the growth velocity during the preceding year was less than 1 cm, and bone age ≥14 yrs.

**Hormone assays**

Serum IGF-1 levels were measured using a radioimmunoassay (IRMA, Nichols Institute Diagnostic, San Juan Capistrano, CA). The sensitivity of the assay was 0.008 nmol/L. Mean intra- and interassay coefficients of variation were 1.8 % and 5 %, respectively.

**Statistical analysis**

Data are expressed as mean ± SEM. Statistical significance was determined by the Wilcoxon signed rank test or the Wilcoxon rank sum test, as appropriate, and by the Kruskal-Wallis One Way ANOVA on Ranks. Statistical significance was set at p<0.05.
RESULTS

Plasma LH and FSH concentrations in response to GnRH stimulation were suppressed in both groups throughout the treatment period and raised to levels appropriate for Tanner stage V of pubertal development within 1.5 yrs from discontinuation of therapy. Menarche occurred $18.2 \pm 4.0$ and $16.3 \pm 2.3$ months after discontinuation of therapy in girls treated with GnRHa and GnRHa plus Ox, respectively, with subsequent regular menses in both groups. Bone age progressed regularly in both groups of patients until epiphyseal closure without any significant difference between groups. At initiation of GnRHa therapy, predicted adult height (PAH) of patients in Group 1 was not significantly different from that computed at the time Ox was added to the treatment. At the end of treatment with GnRHa plus Ox, PAH was significantly higher than that detected at diagnosis and at the start of GnRHa (Table 1). In Group 1 patients, final height significantly exceeded target height, was similar to the PAH recorded at the end of the treatment, and significantly higher than that at the beginning of GnRHa (Table 1) (Fig. 1). In patients in Group 2, PAH at initiation of treatment was not significantly different from that at the end of GnRHa therapy (Table 2). Final height of these patients was similar to the PAH at both the end and the beginning of treatment (Table 2) (Fig. 1). Target height was not reached and it was significantly higher than final height. The difference between final heights and pre-treatment PAH of patients in Group 1 was significantly different from that in Group 2 ($7.8 \pm 2.3 \text{ vs } -3.8 \pm 2.3 \text{ cm}, p<0.02$). The same is true for the difference between final heights and target heights ($4.6 \pm 1.8 \text{ vs } -4.2 \pm 1.1 \text{ cm}, \text{ in Group 1 and 2, respectively, } p<0.005$). No adverse effects were recorded during either GnRHa or GnRHa plus Ox therapy. IGF-1 concentrations were unaffected by treatment in both groups (Group 1: at diagnosis $38.2 \pm 6.2 \text{ nmol/L}$; during GnRHa treatment $36.9 \pm 5.5 \text{ nmol/L}$; during Ox treatment $38.3 \pm 4.6 \text{ nmol/L}$).
nmol/L; Group 2: at diagnosis 40.9 ± 6.1 nmol/L; during GnRHa therapy 46.9 ± 5.9 nmol/L).

DISCUSSION

The results of the present study indicate that in girls with idiopathic CPP and severe growth deceleration during GnRHa treatment, the addition of Ox is able to improve final height without any significant side effect. Combined therapy allowed patients to reach a final height higher than the target height, whereas patients who showed severe growth deceleration but were treated with GnRHa alone attained a final height lower than the target height. This was due to a height gain, computed as the difference between final height and pre-treatment PAH, of 7.8 and -3.8 cm in Groups 1 and 2, respectively. Bone age progressed at the same rate in the two groups, and menarche occurred approximately 1.5 yrs after discontinuation of treatment with subsequent regular menses in both groups of patients.

The primary goal of GnRHa therapy in CPP is to slow pubertal maturation and preserve the height potential. Deceleration in growth is expected during GnRHa therapy, but in some patients the decrease during therapy is so marked to prevent the expected improvement in height. Even after several years of therapy, patients may fail to reach their target heights (4, 6). This observation led to the use of GH in combination with GnRHa to improve final height in children with CPP (6, 8). The published studies do suggest a real benefit from adding GH to GnRHa therapy in children with suboptimal growth during GnRHa therapy. In the two studies in which the adult height of patients with CPP treated with combined GnRHa and GH therapy was reported (6, 8), the mean adult height was 7.1 and 8.1 cm greater that the pre-treatment PAH in the first and second report, respectively, and 3.5 and 4.6 cm greater than the adult height reached by the control groups,
respectively. Results of the present study compare favourably with those obtained by the addition of GH to GnRHa treatment, with a mean adult height 7.8 cm greater than the pre-treatment PAH, and 4.5 cm greater than the adult height reached by the control group. Evaluation of the cost and burden of GH (expensive drug requiring parental administration) versus Ox (cheap and oral administration) treatment, makes the latter unquestionably more convenient to both the patients and the community.

Ox, a nonaromatizable androgen which has a high anabolic to androgenic ratio compared to testosterone (9), has been used to stimulate growth in boys with constitutional delay of growth and puberty (11-13). Small steroid doses induce a sustained growth acceleration without a disproportionate acceleration of skeletal maturation (29), or pubertal maturation. Furthermore, long-term studies have shown that treatment with Ox does not affect final height (30, 31). The precise mechanism of the growth acceleration induced by Ox is still unclear. Studies on the effect of the steroid on the somatotropic axis have provided conflicting results, with some showing a positive effect (14) and others showing no effect at all (15-17). Those showing an increase in GH secretion included few patients with highly variable responses (14, 15). In agreement with previous studies (13), (32), in the present study GnRHa therapy alone or in combination with Ox had no effect on IGF-1 concentrations, further supporting a somatotropic-independent mechanism of action of the steroid.

In the growth plate and at sites of endochondral ossification in the osteophytes, androgen receptors are predominantly expressed by hypertrophic chondrocytes (18), and specific dihydrotestosterone binding sites were demonstrated in cultured human fetal epiphyseal chondrocytes (19). It was documented that androgens regulate both proliferation and differentiation of cultured epiphyseal chondrocytes (19-23) supporting a direct effect of androgens on growth plate cartilage. A direct effect of androgens on epiphyseal growth and maturation is also indicated by the fact that the injection of
testosterone into the growth plate of rats, increases the growth plate width (33). The growth promoting action of Ox may therefore be related to its direct effect on the growth plate cartilage rather than to an activating effect on the somatotropic axis.

In conclusion, combined GnRHa and Ox therapy can improve adult height in children with CPP and deceleration in growth during treatment with GnRHa alone. In such a subset of patients, the improvement in adult height together with the absence of significant side effects make this combination therapy a viable treatment option.

ACKNOWLEDGEMENTS

We thank Mrs. Loredana Arvasi, Cristina Colombini and Aurelia Pantaleo for their technical support.
Table 1. Auxologic features of patients treated with GnRHa plus Oxandrolone

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>At start of GnRHa</th>
<th>At start of GnRHa+Ox</th>
<th>At end of GnRHa+Ox</th>
<th>At final height</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (yr)</td>
<td>6.9 ± 0.3</td>
<td>7.8 ± 0.2</td>
<td>10.7 ± 0.2</td>
<td>12.5 ± 0.2</td>
<td>15.1 ± 0.4</td>
</tr>
<tr>
<td>BA (yr)</td>
<td>8.4 ± 0.6</td>
<td>10 ± 0.2</td>
<td>11.9 ± 0.3</td>
<td>13.1 ± 0.2</td>
<td>16.1 ± 0.2</td>
</tr>
<tr>
<td>BA/CA</td>
<td>1.2 ± 0.03</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.02</td>
<td>1.0 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Tanner stage A</td>
<td>A 0-1</td>
<td>A 0-2</td>
<td>A 1-3</td>
<td>A 2-3</td>
<td>A 3</td>
</tr>
<tr>
<td></td>
<td>P 1-2</td>
<td>P 1-3</td>
<td>P 1-4</td>
<td>P 3-5</td>
<td>P 3-5</td>
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<td></td>
<td>B 2-4</td>
<td>B 3-4</td>
<td>B 1-4</td>
<td>B 1-4</td>
<td>B 4-5</td>
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<tr>
<td>Tanner stage P</td>
<td></td>
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<tr>
<td>Tanner stage B</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Height (SDS for BA)</td>
<td>-0.8 ± 0.3</td>
<td>-0.9 ± 0.3</td>
<td>-0.2 ± 0.5</td>
<td>-0.2 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>PAH (cm)</td>
<td>156.8±2.3</td>
<td>154.8±1.7</td>
<td>158.5±1.8</td>
<td>163.4±2.4</td>
<td></td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>158.0±1.9</td>
<td></td>
<td></td>
<td></td>
<td>162.6±2.3</td>
</tr>
</tbody>
</table>

\(^{a}\): p<0.05 vs At diagnosis; \(^{b}\): p<0.05 vs At start of GnRHa; \(^{c}\): p<0.05 vs target height.

Mean ± SEM

CA: chronologic age; BA: bone age; SDS: standard deviation score; Ox: oxandrolone;

PAH: predicted adult height.

Tanner stage (range): A = axillary hair; P = pubic hair; B = breast development.
Table 2. Auxologic features of patients treated with GnRHa alone

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>At start of GnRHa</th>
<th>At end of GnRHa</th>
<th>At final height</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (yr)</td>
<td>6.7 ± 0.3</td>
<td>6.9 ± 0.3</td>
<td>11.9 ± 0.2</td>
<td>14.4 ± 0.6</td>
</tr>
<tr>
<td>BA (yr)</td>
<td>8.5 ± 0.6</td>
<td>8.8 ± 0.5</td>
<td>12.4 ± 0.3</td>
<td>17.2 ± 0.2</td>
</tr>
<tr>
<td>BA/CA</td>
<td>1.2 ± 0.1</td>
<td>1.3 ± 0.05</td>
<td>1.2 ± 0.04</td>
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<tr>
<td>Tanner stage</td>
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<tr>
<td></td>
<td>A 0-1</td>
<td>A 0-2</td>
<td>A 1-3</td>
<td>A 3</td>
</tr>
<tr>
<td></td>
<td>P 1-2</td>
<td>P 1-2</td>
<td>P 3-4</td>
<td>P 3-5</td>
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<tr>
<td></td>
<td>B 2-4</td>
<td>B 3-4</td>
<td>B 2-4</td>
<td>B 4-5</td>
</tr>
<tr>
<td>Height (SDS for BA)</td>
<td>-1.4 ± 0.2</td>
<td>-1.4 ± 0.2</td>
<td>-1.0 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>PAH (cm)</td>
<td>155.2±2.0</td>
<td>155.4±2.1</td>
<td>157.0±1.2</td>
<td></td>
</tr>
<tr>
<td>Target height (cm)</td>
<td>156.6±1.4</td>
<td></td>
<td></td>
<td>151.9±1.2*</td>
</tr>
</tbody>
</table>

Mean ± SEM

CA: chronologic age; BA: bone age; SDS: standard deviation score; PAH: predicted adult height.

* p<0.005 vs target height.

Tanner stage (range): A = axillary hair; P = pubic hair; B = breast development.
FIGURE LEGEND

- : Predicted height (PAH) at start of GnRHa
- : Target height (TH)
- : Final height (FH)

Mean ± SEM

* p< 0.05 FH of patients treated with GnRHa+oxandrolone vs their PAH and TH.

& p< 0.05 FH of patients treated with GnRH alone vs their TH.
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GnRH alone  GnRH+Oxandrolone

Height (cm)

*