Clonidine Treatment in Children with Non-Endocrine Short Stature

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Abstract. Clonidine stimulates GH release via release of GH releasing hormone from the hypothalamus. There has been controversy as to its usefulness in the therapy of children with constitutional growth delay.

To evaluate the effect of clonidine treatment we administered clonidine (0.1mg/m²) daily for more than 6 months to 31 prepubertal children (20 male and 11 female) and 24 pubertal children (16 male and 8 female) with non-endocrine short stature. Then we analyzed the height velocity (HV), height velocity SD score (HVSD), and height SD score (HSD) as indicators of their growth response to this therapy. Furthermore, we determined the serum levels of IGF-I and IGFBP-3.

In prepubertal children the mean HV and HVSD were increased at 6 months, and remained high thereafter. Four children showed a 2cm increase of HV at 6 months. In pubertal children both HV and HVSD were increased at 6 months, but not increased further. Both IGF-I and IGFBP-3 were significantly increased at 6 months and remained high until 12 months. There was no evidence of accelerated bone maturation or noticeable side-effects.

In conclusion, administration of clonidine could be a useful mode of treatment in some children with non-endocrine short stature because of the low cost and the convenience of oral intake. The administration period should be kept within 6 months at a time.

Key words: clonidine, non-endocrine short stature, height velocity, IGF-I, IGFBP-3
Table 1. Changes in auxological data in prepubertal children

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=31)</th>
<th>Clonidine at 6 mo (n=31)</th>
<th>Clonidine at 12 mo (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height velocity</td>
<td>4.5±1.1</td>
<td>5.1±1.6</td>
<td>5.1±1.1*</td>
</tr>
<tr>
<td>HVSD</td>
<td>-1.5±1.4</td>
<td>-0.6±2.3</td>
<td>-0.6±1.6*</td>
</tr>
<tr>
<td>ΔHV(cm/yr)</td>
<td>0.5±1.7</td>
<td>0.5±1.3*</td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean±SD. *p<0.05 vs baseline

Table 2. Changes in plasma levels of IGF-I and IGFBP-3 in prepubertal children

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=26)</th>
<th>Clonidine at 6 mo (n=26)</th>
<th>Clonidine at 12 mo (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/ml)</td>
<td>175±99</td>
<td>230±103*</td>
<td>187±95</td>
</tr>
<tr>
<td>IGFBP-3 (nmol/l)</td>
<td>180±26</td>
<td>196±36*</td>
<td>183±37</td>
</tr>
</tbody>
</table>

Values represent mean±SD. *p<0.01 vs baseline

Subjects and Methods

Thirty-one prepubertal children (20 boys and 11 girls) and 24 pubertal children (16 boys and 8 girls) with NESS were enrolled. Clonidine was administered orally (0.1mg/m² body surface area), half in the morning and half at bedtime for more than 6 months. Height, bone age, and plasma levels of IGF-I and IGFBP-3 were measured every 6 months. Bone age was assessed according to the method of Greulich and Pyle (1).

Results

Prepubertal children: In prepubertal children, the mean height velocity (HV) was increased after 6 months of clonidine treatment, and remained high thereafter (Table 1). The mean height velocity SD score (HVSD) was also increased after 6 months, but not increased further. Clonidine therapy resulted in an improvement in HV (ΔHV) compared to those values before therapy. However, there was no significant difference in ΔHV between 6 and 12 months. Four of the 31 (13%) children and one of the 19 (5%) children were good responders 6 and 12 months after the begin-

Table 3. Changes in auxological data in pubertal children

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=24)</th>
<th>Clonidine at 6 mo (n=24)</th>
<th>Clonidine at 12 mo (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height velocity</td>
<td>5.6±1.6</td>
<td>6.7±2.7</td>
<td>6.6±3.0</td>
</tr>
<tr>
<td>HVSD</td>
<td>-0.4±2.2</td>
<td>1.0±3.3*</td>
<td>1.2±3.6</td>
</tr>
<tr>
<td>ΔHV(cm/yr)</td>
<td>0.5±1.7</td>
<td>1.1±2.7</td>
<td>1.0±3.0</td>
</tr>
</tbody>
</table>

Values represent mean±SD. *p<0.05 vs baseline

Table 4. Changes in plasma levels of IGF-I and IGFBP-3 in pubertal children

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=15)</th>
<th>Clonidine at 6 mo (n=14)</th>
<th>Clonidine at 12 mo (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/ml)</td>
<td>350±141</td>
<td>440±155*</td>
<td>434±109*</td>
</tr>
<tr>
<td>IGFBP-3 (nmol/l)</td>
<td>179±46</td>
<td>216±36*</td>
<td>218±39</td>
</tr>
</tbody>
</table>

Values represent mean±SD. *p<0.01 vs baseline

ning of treatment, respectively, when an increase in HV greater than 2cm/year is considered significant (2). Furthermore, 13 of the 31 (42%) children and 8 of the 19 (42%) children attained and increase in HV greater than 1cm/year at 6 and 12 months, respectively.

The plasma levels of both IGF-I and IGFBP-3 increased significantly after 6 months of clonidine treatment and decreased thereafter (Table 2).

Pubertal children: In pubertal children, since HV changes according to pubertal development, determining HV for the chronological age is not always useful. Therefore, in this study we investigated the auxological data corrected for bone age (BA). The mean HV was increased after 6 months of treatment, but not any further (Table 3). The mean HVSD was increased significantly until 12 months, but the mean ΔHV was increased after 6 months and remained until 12 months. In these pubertal children, there are no good indices which evaluate the efficacy of growth-regulating therapy. When a ΔHV of more than 2cm/year is considered significant as in prepubertal children, 8 out of 21 (38%) children and 6 out of 17 (35%) children were responders 6 and 12 months after the beginning of treatment, and 14 out of 21 (67%) children and 13 out of 17 (76%) children had an HV greater than that before treatment,
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respectively.

Plasma levels of both IGF-I and IGFBP-3 were increased significantly after 6 months of treatment and continued to increase thereafter (Table 4).

In both the prepubertal and pubertal group there was no correlation between the peak GH response to clonidine stimuli and improvement of ΔHV. We could not find any other factors which predict the response to clonidine treatment in this clinical trial. There was no evidence of accelerated bone maturation or apparent side effects in either prepubertal or pubertal groups.

Comments

Several studies showed that the daily administration of clonidine accelerates the linear growth in short children. In 1985 for the first time Pintor et al. reported that in four children with CGD treated with clonidine, 0.1mg/m² daily, basal GH and IGF-I were increased, the pituitary GH response to challenges with GH releasing factor 40 and clonidine was enhanced, and the linear growth was stimulated (3). Later, Castro-Magana et al. showed that clonidine administration induced increment in the growth hormone levels, plasma IGF-I, and linear growth rate for one year in 16 prepubertal children with CGD (4). Furthermore, Pintor et al. reported that in 34 pubertal children with CGD, one year of clonidine treatment stimulated height velocity and classified those children as clonidine responders on the basis of an increment in ΔHV>2cm/yr. Moreover, they demonstrated that a high HSD and low HV before treatment were predictive of a good growth response to clonidine (5). In 1989, Loche et al. demonstrated the increase in integrated GH after 2 months of clonidine administration and suggested that it resulted from an increased GH pulse amplitude during the awake hours (6). In 1991 Esteban et al. compared the effect of clonidine treatment to a vitamin (considered as a placebo) treatment and suggested its usefulness to treat prepubertal children with CGD. Furthermore, they also classified these children into responders and non-responders on the basis of an increment in ΔHV>2cm/yr and demonstrated that 65% of their patients were responders (7). Volta et al. reported that clonidine induced an increase in HV in prepubertal children with normal short stature significantly different from that in control children (8).

On the other hand, in 1988 Pescovitz demonstrated no sustained increases in GH production, or levels of IGF-I and no improvement in HV with clonidine treatment in a double-blind, placebo-controlled, crossover study (9). In 1993, Allen reported the same findings in ten prepubertal children and suggested that the proposed clonidine-induced increase in endogenous GH secretion either did not exist or does not act as an effective growth-promoting stimulus (10).

Actually there were some children who responded to clonidine treatment on the basis of an increment in ΔHV>2cm/yr in both prepubertal and pubertal stages although our study was not performed as a double-blind, placebo-controlled trial. We also demonstrated the improvement of HVSD in both groups when we evaluated the auxological data corrected for BA in pubertal patients. Moreover, in prepubertal children the plasma levels of IGF-I and IGFBP-3 apparently increased after 6 months of clonidine therapy and declined thereafter. These changes in GH-dependent peptides can not be explained by aging per se. Therefore, we consider the improvement of ΔHV and HVSD to be the result of clonidine-induced GH secretion.

In conclusion, administration of clonidine may be useful in some children with NESS because of its low cost and the convenience of oral intake. The period might be limited to within 6 months at a time, particularly in prepubertal children, because the improved HV and HVSD and increased plasma levels of IGF-I and IGFBP-3 after 6 months of clonidine therapy declined thereafter. A longer follow-up study is warranted to determine the effects
of this therapy on adult height and also to
determine which patients respond to this
treatment.

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