Instant growth inhibition by low dose oestrogens in excessively tall boys

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Abstract. A major problem in the androgen treatment of excessive height in boys is acceleration of growth velocity especially in the early stages of therapy. Oestrogen treatment in tall girls, in contrast, instantly decelerates growth velocity, probably by its plasma somatomedin lowering effect. As oestrogen administration in male subjects causes a similar somatomedin depression and immediate growth inhibition is also wanted in the treatment of excessive height in boys, the effect of short-term low dose oestrogen therapy (ethinyloestradiol, Ee, Lynoral®, 0.050 mg daily) on growth was studied in 10 constitutionally tall boys. During oestrogen therapy three week ulnar growth rate (TUG-rate) dropped instantly from 0.84 ± 0.42 to 0.33 ± 0.27 mm (P < 0.02) within 6 weeks. Three week body growth rate also changed significantly from 0.48 ± 0.23 to 0.12 ± 0.37 cm during oestrogen loading (P < 0.05). The magnitude of the latter changes, however, allows only evaluation of the whole group, whereas changes in TUG-rates far exceeded the limits of confidence in most individual boys. Growth deceleration during Ee was accompanied by a significant decrease in serum alkaline phosphatase activities (from 299 ± 72 U/l before to 240 ± 79 U/l during Ee, P < 0.01), plasma calcium (from 2.45 ± 0.06 to 2.35 ± 0.05 mmol/l during Ee, P < 0.05) and plasma testosterone levels (from 392 ± 128 ng/100 ml before to 27 ± 7 ng/100 ml during Ee, P < 0.005). Within 2 months after stopping Ee administration plasma testosterone levels were normal again (432 ± 282 ng/100 ml).

Testicular size was not affected. Mild reversible gynaecomastia, however, was present in all boys. The results demonstrate an instant growth decelerating effect of low dose oestrogen administration in tall boys reminiscent to the findings in tall girls under the same low dose regimen. Furthermore these data provide a theoretical base for combining androgens and oestrogens in the early stages of treatment of excessive height in boys in order to antagonize the initial growth accelerating effect of androgens alone.

In contrast to many reports on oestrogen treatment of excessively tall girls (for review Wettenhall et al. 1975; New et al. 1978) only few papers deal with hormonal growth inhibition in tall boys (Whitelaw et al. 1965; Ruvalcaba et al. 1975; Zachmann et al. 1976; Bierich 1978). Like oestrogens in tall girls, testosterone treatment in tall boys has proven to be successful in reducing final body height with regard to predicted height. A major problem, however, in testosterone therapy is acceleration of growth velocity in the early stages after starting androgen administration (Bierich & Schönberg 1975; Marshall 1977), particularly in the younger bone age group (Zachmann et al. 1975). Since serious psychological problems are the main indication for sex hormone treatment in most cases, acceleration of growth velocity is hardly acceptable when growth inhibition is wanted.

Oestrogen therapy in tall girls, however, decelerates growth velocity instantly in most of the patients (Zachmann et al. 1975; Prader & Zachmann 1978) even in low doses (van den Bosch et al. 1981), probably by its somatomedin lowering effect.

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(von Puttkamer et al. 1975, 1977). This decrease of plasma somatomedin by oestrogens has also been demonstrated in male subjects (Wiedemann et al. 1976; Clemmons et al. 1980). In contrast to oestrogens, the effect of androgens on growth velocity is regarded to be independent of somatomedin and probably mediated by their anabolic action per se (van den Brande & Du Caju 1974; Philips & Vassilopoulou-Sellin 1980). These latter actions may temporarily increase growth velocity in concert with elevated growth hormone levels (Martin et al. 1968; Aynsley-Green et al. 1976), an undesired effect in the treatment of excessively tall boys. To overcome this initial growth accelerating effect of androgens — which occurs despite substantial peripheral aromatization of oestrogens (Santen 1975; Matsumoto et al. 1981) — the effect of low dose oestrogen therapy on short-term growth was studied in boys with constitutional tall stature, using the sensitive ulnar length measuring technique.

Materials and Methods

Ten constitutionally tall boys volunteered to participate in this study after obtaining informed parental consent. Data on growth and development are tabulated in Table 1 illustrating that the study was performed on randomly chosen excessively tall boys who were still growing. This enabled evaluation of the instant growth inhibiting effect of ethinyloestradiol (Lynoral®, Organon) on short-term growth in all stages of pubertal development and growth spurt. Due to the short-term character of this study no conclusions could be made on the actual reduction of final body height vs predicted height.

All boys received 0.050 mg ethinyloestradiol over a period of at least 6 weeks. Mean growth velocities were assessed over periods of exactly 6 weeks before and immediately after starting and stopping of Ee administration. Measurements were performed at the beginning and the end of the respective periods in all boys exactly at 6 week intervals. Some boys received Ee up to 6 months in order to evaluate possible side effects.

Ulnar growth velocities were measured using the non-invasive ulnar length measuring technique developed and described by Valk (1971, 1972) and recently by van den Bosch et al. (1979) which enables accurate measurement of short-term growth (Valk 1972; Valk & van den Bosch 1978; van den Bosch et al. 1981). Each ulnar length determination comprised six successive independent measurements by the same observer. The mean SD of the samples in this study amounted to 0.20 mm implying a mean SE of 0.08 mm. Growth in ulnar length was expressed as the three week ulnar growth rate in mm, i.e. TUG-rate.

Growth in body height was determined using the Harpenden stadiometer and was expressed as the 3 week body growth rate in cm.

Since the results of both ulnar length and body height measuring techniques are influenced by diurnal variation in length (Whitehouse et al. 1974; Valk & van den Bosch 1978) all measurements in each individual were performed at exactly the same moment of the day throughout the whole study period and by the same observer.

Blood for serum alkaline phosphatase activities, plasma calcium, phosphorus and testosterone levels was sampled before, during and after ethinyloestradiol administration.

Serum alkaline phosphatase activities were measured using the Bessy and Lowry technique adapted to automated analysis (Bessy et al. 1946). Plasma calcium and phosphorus were determined using routine laboratory techniques. Plasma testosterone was assayed after a paper chromatographic purification step using an antiserum generated in rabbits against 11-hydroxytestosterone hemisuccinate conjugated to albumin (Smals et al. 1976).

Mean values are given ± 1 SD.

Table 1

Characteristics on growth and development in 10 constitutionally tall boys at the start of the study.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± sd</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calendar age</td>
<td>14.5 ± 1.37</td>
<td>12.5-16.0</td>
</tr>
<tr>
<td>Bone age¹ (years)</td>
<td>13.5 ± 0.9</td>
<td>12.5-15.0</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>190 ± 6.9</td>
<td>176.5-203.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.3 ± 8.2</td>
<td>52.9-77.0</td>
</tr>
<tr>
<td>Testicular size (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>length</td>
<td>4 ± 1.1</td>
<td>1.5-5.5</td>
</tr>
<tr>
<td>width</td>
<td>3 ± 0.6</td>
<td>2-4</td>
</tr>
<tr>
<td>Tanner stage</td>
<td>II-V</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>404 ± 215</td>
<td>13-790</td>
</tr>
</tbody>
</table>

The changes in mean (●—●) and individual (●—○) three week ulnar growth rates (TUG-rates) in 10 constitutionally tall boys. The left panel refers to the changes in TUG-rates during 6 weeks of ethinylestradiol (EOe) administration (Lynoral®, 0.050 mg daily, n = 10). The right panel reveals the changes in TUG-rates during 6 weeks after stopping EOe in 9 of them. Individual subjects are indicated by number.

Results

The effect of ethinylestradiol (Ee) on growth velocity (Fig. 1)

The left panel of Fig. 1 reveals the changes in mean and individual TUG-rates during 6 weeks of Ee administration (0.050 mg/day). The mean TUG-rate decreased significantly from 0.84 ± 0.42 mm before to 0.33 ± 0.27 mm during Ee treatment (P < 0.02). In 8 of the 10 boys the decrease in TUG-rate was above the limit of confidence (3 × SE).

Three week body growth-rate also decreased significantly from a mean pre-treatment value of 0.48 ± 0.23 to 0.12 ± 0.37 cm during Ee administration (P < 0.05). Body weight did not change significantly during Ee loading (P > 0.10).

The effect of stopping ethinylestradiol (Ee) administration (Fig. 1)

The right panel of Fig. 1 refers to the changes in mean and individual TUG-rates after stopping the Ee loading. Mean TUG-rate increased from 0.28 ± 0.32 mm during to 0.53 ± 0.27 mm after stopping Ee. Although there was a tendency this

Fig. 2.

The changes in mean (●—●) and individual (●—○) serum alkaline phosphatase activities, plasma calcium and phosphorus levels in relation to the changes in three week ulnar growth rates (TUG-rates) in tall boys. The left panel refers to the changes during 6 weeks of ethinylestradiol (EOe) administration (Lynoral®, 0.050 mg daily). The right panel illustrates the changes during the 6 weeks after stopping EOe. Individual subjects are indicated by number.
difference lacked statistical significance (0.10 > \( P > 0.05 \)). Ulnar growth velocities before and after Ee administration differed neither significantly (\( P > 0.10 \)).

No changes in body growth rate and body weight were found during this part of the study (\( P > 0.10 \)).

**The effect of ethinyl oestradiol (Ee) on biochemical phenomena** (Fig. 2)

In Fig. 2 the changes in individual and mean serum alkaline phosphatase activities, plasma calcium and phosphorus levels are depicted in relation to the changes in TUG-rates. The left panel shows the changes during Ee administration, whereas the right panel reveals the changes after stopping Ee.

Serum alkaline phosphatase activities decreased significantly from a mean level of 299 ± 72 U/l before to 240 ± 79 U/l during Ee loading (\( P < 0.01 \), \( n = 8 \)). After stopping Ee administration the mean phosphatase activities changed from 215 ± 92 to 240 ± 90 U/l. This increment was not statistically significant (\( P > 0.10 \), \( n = 7 \)). Post-treatment phosphatase levels tended to be lower than pre-treatment activities (0.10 > \( P > 0.05 \)).

Mean plasma calcium decreased during Ee loading from 2.45 ± 0.06 to 2.35 ± 0.05 mmol/l (\( P < 0.05 \), \( n = 5 \)). After stopping Ee the mean plasma calcium increased from 2.36 ± 0.06 to 2.42 ± 0.07 mmol/l. Although there was a tendency this increment was not statistically significant (0.10 > \( P > 0.05 \), \( n = 5 \)).

In contrast to plasma calcium and serum alkaline phosphatase activities, there were no significant changes in plasma phosphorus (1.35 ± 0.18 mmol/l before vs 1.32 ± 0.23 mmol/l during Ee, and 1.34 ± 0.19 mmol/l during vs 1.30 ± 0.20 mmol/l after stopping Ee loading, \( P > 0.10 \), \( n = 5 \)).

During Ee treatment plasma testosterone levels fell from a pre-treatment value of 392 ± 128 to 27 ± 7 ng/100 ml (\( P < 0.005 \), \( n = 5 \)). Within 2 months after stopping Ee loading testosterone levels had increased again to normal values (432 ± 282 ng/100 ml, \( P < 0.05 \), \( n = 5 \)). Two of these 5 boys were treated for 6 weeks, 2 for 4 months and one for 6 months.

**The effect of ethinyl oestradiol (Ee) on testicular size and mammary gland tissue**

In none of the 10 boys testicular size was markedly reduced during Ee therapy. The only change observed was a slight weakening of the testis in the boys treated for 4 to 6 months.

The effect on mammary gland tissue was more overt. Eight boys developed moderate gynaecomastia within 6 weeks of Ee administration, 2 boys only after longer treatment. Gynaecomastia remained within acceptable limits for the patients and disappeared after stopping Ee treatment within 2 months.

**Discussion**

This study demonstrates for the first time the instant growth inhibiting effect of low dose oestrogens in tall boys. The significant decrease of ulnar growth rate in response to this low dose of ethinyl oestradiol (Ee) was almost identical to that found in tall girls (van den Bosch et al., in press). In both groups of tall girls and boys studied, body growth rate also decreased significantly during oestrogen therapy. However, the magnitude of the changes in body height allows only evaluation for the whole group, whereas the changes in TUG-rates far exceeded the limit of statistical confidence (3 ± se) in nearly all individual youngsters.

After stopping Ee administration ulnar growth rates tended to increase again, a phenomenon also observed in tall girls. Both the decelerating effect during Ee and the acceleration after stopping Ee might be in accordance with the proposed mechanism of action of oestrogens on plasma somatomedin levels, which is well documented in literature for both sexes (van Puttkamer et al. 1975, 1977; Wiedemann et al. 1976; Clemmons et al. 1980). A second mechanism accounting for the growth inhibition in these boys might be direct or indirect oestrogen mediated suppression of Leydig cell function (Yanaihara et al. 1972; Smals et al. 1974, 1980; Jones et al. 1978) illustrated by the overt fall of plasma testosterone levels to pre-pubertal values during treatment. Finally both mechanisms may simultaneously contribute to growth inhibition in boys. Mere growth hormone suppression as the cause of the instant growth inhibition can be ruled out since oestrogens have been reported to even increase circulating hGH levels, probably due to the positive feedback of somatomedin reduction (Bierich 1978).

This study on short-term growth clearly demonstrates that also in tall boys low doses of oestrogens are effective in instantly reducing growth velocity.
Very recently the growth inhibiting effect of low dose oestrogens was confirmed in a long-term study in tall girls (van der Werff ten Bosch & Bot 1981).

The decrease in growth rate during Ee was also reflected by a significant reduction of serum alkaline phosphatase activities and plasma calcium levels, similar to that found in girls (van den Bosch et al., in press). In contrast to this latter study the plasma phosphorus levels did not change significantly in the boys, probably due to the smaller number of data available. The reduction of serum alkaline phosphatase activities during Ee is opposite to the rise observed during human chorionic gonadotrophin (hCG) induced growth stimulation (van den Bosch et al. 1979 and in press) and therefore probably reflects diminished bone growth (Round et al. 1979). The small but significant decrease in plasma calcium levels during Ee might be explained by a depressive effect of oestrogens on cholecalciferol synthesis (Baksi & Kenny 1978) or on circulating albumin (Kamyab et al. 1978), but is more likely related to diminished skeletal growth during Ee.

Testicular size was not affected during Ee administration in this study and Leydig cell function was only temporarily suppressed as illustrated by the rapid recovery of plasma testosterone levels after stopping Ee. An essential issue to be discussed is the hazard of potential infertility due to oestrogen treatment in men. As in testosterone treatment (Zachmann et al. 1976; Prader & Zachmann 1978) oestrogens cause oligo-azoospermia but under both drug regimens infertility has been reported to be reversible in animals and men using even much higher doses of oestrogens (Heller et al. 1958; Kalra & Prasad 1969; Neumann et al. 1970; Briggs & Briggs 1974; Schoysman 1976).

Although gynaecomastia was manifest, it was mild and reversible in all boys. Together these data illustrate that low dose oestrogen therapy in boys results in instant growth deceleration which to our opinion is an important psychological advantage in the early management of tall stature in boys. Moreover the findings provide a theoretical base for temporarily combining androgens and oestrogens in the early stages of treatment in tall boys in order to antagonize the initial growth accelerating effect of androgens alone.

References


Received on July 16th, 1981.