Treatment of constitutional growth delay in prepubertal boys with a prolonged course of low dose oxandrolone

A Papadimitriou, S Wcharasindhu, K Pearl, M A Preece, R Stanhope

Abstract
Forty six prepubertal boys who had constitutional growth delay were treated with oxandrolone. Mean age at the onset of treatment was 11.9 years (range 9.0-14.0) and bone age delay was 1.9 ‘years’. The dose of oxandrolone used was a mean of 0.05 mg/kg (range 0.03-0.18) for a mean of 0.9 years (range 0.2-3.6). Height velocity increased from a mean (SD) before treatment of 4.0 (1.0) to 7.5 (1.2) cm/year with oxandrolone. Growth rate was sustained at 7.6 (2.2) cm/year in the period after treatment. Those boys who attained a testicular volume of 4 ml or greater at the end of the treatment period had the most pronounced sustained growth acceleration. Height for bone age SD score did not alter significantly from a mean of -1.0 before treatment to -1.2 after treatment.

Oxandrolone is a safe and effective treatment for prepubertal boys with constitutional growth delay.

Oxandrolone is an anabolic steroid that is effective in a low dose regimen for the treatment of constitutional delay of growth and puberty. This is not a placebo effect and does not decrease final height. For psychological reasons such children may require treatment to improve their short term growth rate at an earlier stage of sexual maturation than would be expected for the spontaneous growth spurt of puberty. Treatment alters the ‘tempo’ of their growth without altering final height prognosis.

By definition, constitutional delay of growth and puberty requires short stature, delay of epiphysial maturation, and pubertal delay (>2 SD). However, children who will progress to develop constitutional delay of growth and puberty can often be predicted at a much earlier age by their pattern of bone age maturation and growth delay (which we have described as constitutional growth delay). We believe it is important to treat such children at an early stage in order to anticipate and prevent more severe psychological problems during puberty. During the pubertal growth spurt growth is dependent on a combination of growth hormone and sex steroids. We have substituted the latter by the use of an anabolic steroid in order to improve short term growth rate, and hopefully to induce a sustained growth acceleration, and to anticipate the boys’ stature falling below the normal range at an age when emotional, educational, and physical development is at a premium. Recent data has pointed to the important psychological sequelae of constitutional delay of growth and puberty and we have attempted to anticipate some of these problems.

Patients and methods
Clinical data from 46 patients with constitutional growth delay are shown in the table. Mean age for the onset of treatment was 11.9 years, which is almost the mean age for the onset of puberty in normal boys. The height of all the boys was below the 3rd centile for chronological age, although one was just below the 10th centile. All had symptoms of psychological disturbance, which related to their short stature. Eight boys had mild asthma but had not been treated with systemic corticosteroids. None of the boys had any other medical disorders.

Most of the boys commenced oxandrolone treatment in a dose of 1.25 mg daily, although some (n=5) started at 2.5 mg per day. This calculated at a mean dose of 0.05 mg/kg (range 0.03-0.18). Duration of treatment was 0.9 years (range 0.2-3.6). Treatment was continued either until a 4 ml testicular volume was attained or until a satisfactory increment in height had been gained and the patient did not wish to continue treatment.

Growth was measured by standard anthropometric techniques and bone age measured by the method of Tanner et al. Testicular volume was assessed using a Prader orchidometer and with experience 2, 3, and 4 ml volumes could be distinguished. Height SD score for bone age related height and epiphysial maturation to the

Clinical and growth data on 46 prepubertal boys with constitutional growth delay treated with low dose oxandrolone. Results are mean (range) except for height SD score

<table>
<thead>
<tr>
<th></th>
<th>Before treatment (n=46)</th>
<th>During treatment (n=46)</th>
<th>After treatment (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronological age at onset of treatment (years)</td>
<td>-1.0 (0.2 to 3.3)</td>
<td>0.9 (0.2 to 3.6)</td>
<td>0.8 (0.2 to 1.8)</td>
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<tr>
<td>Bone age delay (years)</td>
<td>-1.0 (0.2 to 3.6)</td>
<td>0.8 (0.2 to 3.6)</td>
<td>-1.2 (-3.7 to 1.3)</td>
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<tr>
<td>Time from start of treatment to onset of puberty (years)</td>
<td>0.8 (0.25 to 3.6)</td>
<td>0.8 (0.25 to 3.6)</td>
<td>0.8 (0.25 to 3.6)</td>
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<tr>
<td>Height SD score for bone age</td>
<td>-1.0 (-3.0 to +1.7)</td>
<td>-1.0 (-3.0 to +1.7)</td>
<td>-1.0 (-3.0 to +1.7)</td>
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<tr>
<td>Mean (SD) change in height SD score for bone age from values before treatment</td>
<td>-0.2 (0.8)</td>
<td>-0.2 (0.8)</td>
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<tr>
<td>p Value</td>
<td>&gt;0.5</td>
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Results

During oxandrolone treatment growth velocity increased from a mean (SD) of 4-0 (1-0) to 7-5 (1-2) cm/year, which was significant to a level of

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oxandrolone for 3-6 years and demonstrated an appropriate advance in his epiphyseal maturation. None of the boys experienced adverse reactions during their course of treatment.

Discussion

Oxandrolone in prepuberty caused an effective increase in growth rate that was at a higher level in those boys who entered puberty during their course of oxandrolone treatment. Normal boys would not expect the commencement of their growth spurt to be until the attainment of 10 ml testicular volume (genitalia stage 3-4). Boys with constitutional delay may experience enormous psychological difficulties associated with their delayed puberty and growth. In our group of patients the latter was effectively treated, anticipating the former. There was no significant decrease in height for bone age SD score. Our data suggest that such a prolonged course of oxandrolone (mean duration almost one year) does not alter final height prognosis and that such treatment enables boys to achieve their expected final height at an earlier age. Indeed one boy was treated with low dose oxandrolone for 3-6 years without a reduction in final height prognosis.

We propose that when it is possible to diagnose constitutional growth delay in a boy who will almost certainly develop delayed puberty then a prolonged course of low dose oxandrolone is an effective treatment regimen. This may allow an earlier growth acceleration and hopefully achieve a height within the normal range at such a critical time for emotional, educational, as well as physical development. Certainly we do not believe that this form of treatment leads to any decrease in final height attainment. The cessation of treatment should be at the attainment of a testicular volume of 4 ml or greater, at which time the growth spurt induced by low dose oxandrolone treatment should be sustained.

Although short courses of oxandrolone are effective in the treatment of constitutional delay of growth and puberty, prolonged courses of oxandrolone, for about one year, are required in prepubertal boys with constitutionally delayed growth. Such longer courses do not lead to adverse side effects, as indeed such prolonged courses appear to be safe when used in girls with Turner’s syndrome. An alternative treatment regimen would be to use depot or oral testosterone preparations. The latter are irregularly absorbed from the gastrointestinal tract and the former may lead to a rapid induction of secondary sexual characteristics as well as an induced growth acceleration. In our experience the psychological benefits of a prolonged course of oxandrolone are significant and such treatment regimens are safe and effective.