

## Double blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty

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**SUMMARY** Nineteen boys, mean age 14.4 years (range 12.9–16.3), with constitutional delay of growth and puberty were randomised into two groups in a double blind fashion for a three month period. Ten boys received oxandrolone, 2.5 mg per day (mean dose 0.072 mg/kg/day), and nine boys were treated with placebo. Mean growth velocity increased from 4.5 cm/year in the oxandrolone treated group to 9.6 cm/year in three months, and this was sustained at 8.6 cm/year after cessation of treatment. In the placebo treated group, growth rate showed no alteration from 5.1 cm/year to 5.2 cm/year; boys in this group were then treated with oxandrolone, 2.5 mg a day (mean dose 0.073 mg/kg/day) for three months and growth velocity accelerated to 8.6 cm/year. Serum concentrations of insulin-like growth factor -1/somatomedin-C (IGF-1) increased during oxandrolone treatment and continued to rise after treatment had ceased. There was no change in serum IGF-1 concentration during treatment with placebo. Oxandrolone, when used in an appropriate regimen, is an effective, safe treatment for boys with constitutional delay of growth and puberty.

We have previously shown that the anabolic steroids fluoxymesterone<sup>1</sup> and oxandrolone<sup>2</sup> are effective in low dose, three month regimens in the treatment of constitutional delay of growth and puberty in boys. Low dose, short course regimens of these anabolic steroids do not result in the inappropriate advancement of epiphyseal maturation<sup>1,2</sup> that undoubtedly occurs when higher doses are used.<sup>3</sup> There has been criticism, however, that in the low dose regimen used, the increase in growth rate observed might have been due to the onset of the spontaneous growth acceleration of puberty or to a placebo effect.<sup>4</sup> The absence of an appreciable effect on epiphyseal maturation could have made the latter a possibility but Sobel has indicated that the effect of anabolic steroids on epiphyseal maturation is dose dependent whereas the effect on growth is not.<sup>5</sup> We have investigated both possibilities by the use of a double blind placebo controlled trial of oxandrolone.

### **Patients and methods**

Nineteen boys, mean age 14.4 years (range 12.9–

16.3), with constitutional delay of growth and puberty were recruited from the growth clinic at The Hospital for Sick Children, Great Ormond Street. All boys had findings consistent with constitutional delay of growth and puberty<sup>6</sup>; all had delayed puberty, height below the third centile for chronological age, and delayed skeletal maturation (mean bone age delay 2.0 'years'). All had experienced psychological difficulties associated with their short stature but none had received psychiatric treatment. Approval was obtained from the Standing Committee on Ethical Practice at the hospital and written parental consent obtained. Approval was only granted for three month treatment periods as longer duration of placebo treatment was considered unethical for boys with delayed puberty whose reason for treatment was psychological distress. As oxandrolone has no product licence in the United Kingdom approval for this trial was obtained from the Department of Health and Social Security.

The study was double blind, placebo controlled and was conducted in parallel on two groups of boys. At the start of treatment boys were randomly allocated into two groups: group A (n=10) and

group B (n=9). Chronological age and bone age delay between the two groups were similar (table). Only one boy from each group had attained stage 3 genitalia; the other boys had genitalia maturation at stage 2. Mean testicular volume was similar in both groups, a mean of 4.9 ml in group A and 4.7 ml in group B. Mean (SD) pretreatment growth velocity was 4.5 (0.8) cm/year in group A and 5.1 (1.7) cm/year in group B which were not significantly different ( $p>0.1$ ). Boys in group A were treated with one 2.5 mg tablet of oxandrolone/day for a mean of 0.25 years (range 0.21–0.28). Boys in group B received one placebo tablet/day for a mean of 0.27 years (range 0.23–0.41). Boys in both groups were directed to take the tablets during the early evening. For ethical reasons the code was broken after the first three month anthropometric assessment. Boys who had received placebo (group B) were offered oxandrolone 2.5 mg daily for three months, and all accepted. Group A, who had been treated with oxandrolone, received no further treatment during the second three months except for one boy who had no growth response and was given a further three month course of oxandrolone of 2.5 mg/day. The mean dose of oxandrolone was 0.072 mg/kg/day (range 0.057–0.097) in group A and 0.073 mg/kg/day (range 0.051 to 0.088) in group B. None of the boys experienced side effects related to oxandrolone treatment.

Stature was measured by standard anthro-

pometric techniques using a stadiometer at intervals of three months.<sup>7</sup> Pubertal maturation was assessed by the method described by Tanner.<sup>8</sup> Testicular volume was measured using an orchidometer.<sup>9</sup> Venous blood was drawn from all patients at the end of the pretreatment, first, and second treatment periods. Serum IGF-1 concentration was measured by radioimmunoassay after acid-ethanol extraction.<sup>10</sup> Antiserum R557A and [<sup>125</sup>I]IGF-1<sup>11</sup> were provided by Dr D J Morrell, Institute of Child Health, London. IGF-1 values were expressed as potency relative to pooled normal adult human reference serum defined as 1 unit IGF-1/ml. Intra-assay and interassay coefficients of variation were <8% and <10%, respectively. Statistical analysis was by paired and unpaired *t* tests.

## Results

Treatment periods and rates of progression of sexual maturation were identical in both groups. Growth data from groups A and B are shown in fig 1. Growth velocity increased from a mean of 4.5 cm/year to 9.6 cm/year ( $p<0.001$ ) after three months of oxandrolone treatment (group A) and this was sustained at 8.6 cm/year ( $p<0.001$ ) after treatment had ceased. One boy did not have a growth acceleration during three months of oxandrolone treatment but did so during a further three months treatment; we do not know if this was due to

Table Pretreatment clinical data from 19 boys with constitutional delay of growth and puberty

	Patient No	Chronological age (years)	Bone age delay (years)	Genitalia stage	Testicular volume (ml)
<b>Group A</b>	1	13.4	1.0	2	04/04
	2	15.9	1.4	3	08/08
	3	15.0	0.8	2	04/04
	4	13.2	1.3	2	04/04
	5	12.9	2.5	2	05/05
	6	13.7	0.9	2	06/06
	7	13.9	0.6	2	05/05
	8	15.1	4.2	2	05/05
	9	16.3	1.5	2	06/05
	10	13.3	2.6	2	03/03
Mean (range)		14.3 (12.9–16.3)	1.7 (4.2–0.6)		4.9 (3–8)
<b>Group B</b>	1	13.5	3.1	2	05/04
	2	14.1	3.0	2	03/03
	3	13.3	2.4	2	05/04
	4	13.5	0.8	2	04/04
	5	16.2	3.1	2	05/04
	6	14.7	2.6	2	04/04
	7	15.4	1.4	2	06/06
	8	14.2	2.5	3	06/06
	9	15.0	1.8	2	06/06
Mean (range)		14.4 (13.3–16.2)	2.3 (3.1–0.8)		4.7 (3–6)

inadequate duration of treatment, measurement error, or non-compliance. The only boy in group A who had a testicular volume of <4 ml did not have a sustained growth acceleration. We have previously described the attainment of testicular volume of >4 ml as a prerequisite for an oxandrolone induced, sustained growth spurt.<sup>2</sup> The group who received placebo (group B) had no significant change in growth velocity; a mean of 5.1 cm/year increased to 5.2 cm/year ( $p>0.5$ ) after three months. Subsequent

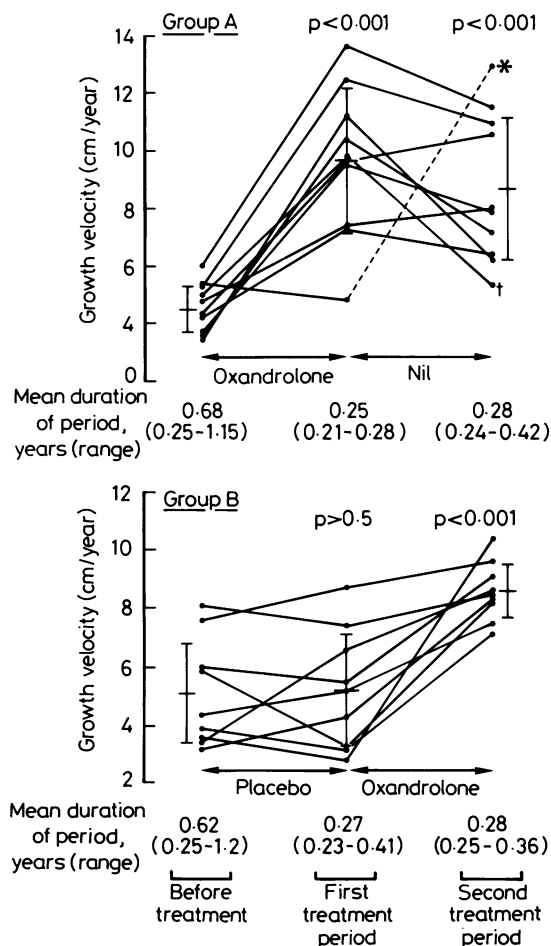


Fig 1 Growth velocity in groups A ( $n=10$ ) and B ( $n=9$ ) during pretreatment, first, and second treatment periods. Mean duration of each period (range) are given. The horizontal bars represent the mean (SD). One boy (\*) in group A did not respond to oxandrolone in the first three months and received a further three months course (broken line). One boy (†) had a testicular volume of <4 ml.

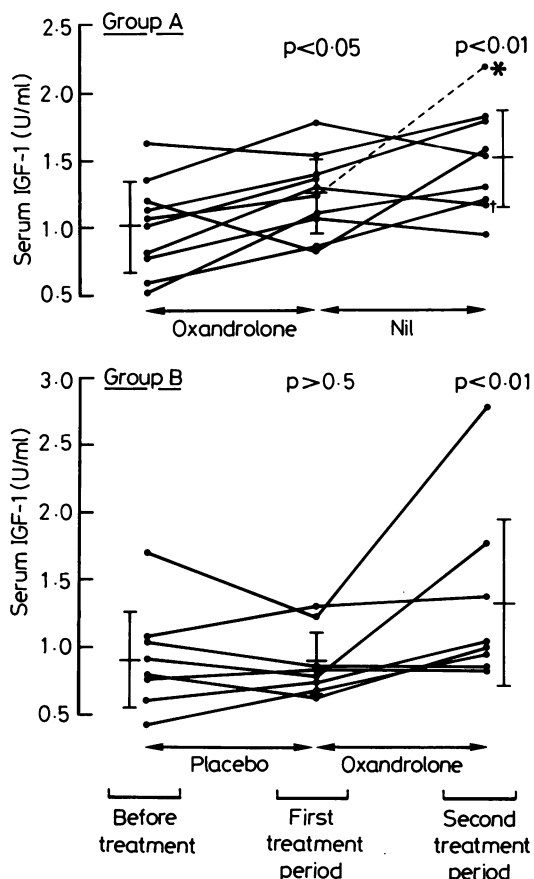


Fig 2 Serum IGF-1 concentration in groups A and B during pretreatment, first, and second treatment periods. The horizontal bars represent the mean (SD). One boy (\*) in group A did not respond to oxandrolone in the first three months and received a further three month course (broken line). One boy (†) had a testicular volume of <4 ml.

treatment of group B with oxandrolone resulted in growth acceleration to a mean of 8.6 cm/year ( $p<0.001$ ).

Serum IGF-1 concentrations are shown in fig 2. In group A, mean serum IGF-1 concentration increased from a mean of 1.01 U/ml to 1.23 U/ml ( $p<0.05$ ) during oxandrolone treatment and further increased to 1.49 U/ml ( $p<0.01$ ) during the post-treatment period. In group B there was no significant change in serum IGF-1 from a mean of 0.90 U/ml to 0.88 U/ml ( $p>0.5$ ) on placebo, although there was an increase to 1.33 U/ml ( $p<0.01$ ) after oxandrolone treatment.

## Discussion

We have shown in this study that oxandrolone produced a growth acceleration in boys with constitutional delay of growth and puberty that was sustained in the post-treatment period. This was not a placebo effect. The level of attainment of sexual maturation was insufficient to cause the spontaneous growth acceleration of puberty and consequently the growth acceleration achieved was due to oxandrolone. Indeed, this sustained growth acceleration becomes indistinguishable from the spontaneous growth spurt of puberty<sup>12</sup> at the attainment of stage 3 to 4 genitalia<sup>13</sup> or 10 ml testicular volume.<sup>14</sup> Low dose oxandrolone advanced the timing of the growth spurt with little, or no, interference in the rate of progress of sexual maturation. Certainly there was no clinical evidence of suppression of the hypothalamo-pituitary-gonadal axis (reduction in testicular volume) which has been associated with the administration of larger doses of anabolic steroids.<sup>15</sup>

We believe that oxandrolone, used in the regimen we have described, is an effective and safe treatment for constitutional delay of growth and puberty in boys. None of the boys experienced side effects due to oxandrolone treatment. As the growth response to anabolic steroids is not dose dependent,<sup>5</sup> lower doses than we have used in this study may be as effective.<sup>16</sup> Other potential treatment modalities for constitutional delay of growth and puberty, such as depot testosterone or biosynthetic human growth hormone, may not be as effective as oxandrolone. The former may produce inappropriate advancement of epiphyseal maturation, the latter is very expensive; both have to be given by injection.

We have previously hypothesised that the sustained growth acceleration induced by oxandrolone is caused by a sustained increase in growth hormone secretion.<sup>2</sup> Anabolic steroids increase the growth hormone response to insulin induced hypoglycaemia<sup>17</sup> and the growth hormone response to growth hormone releasing factor.<sup>18</sup> Our serum IGF-1 data point to increased growth hormone secretion induced by oxandrolone and this would explain the sustained pattern of the growth acceleration. This is in addition to a direct action on the tissues which is probably the predominant effect of oxandrolone in prepubertal children.

The response to oxandrolone, in the dose regimen used, was neither due to placebo effect nor due to the spontaneous growth acceleration of puberty. Anabolic steroids originally came into disrepute because they were used in high dose, long duration courses which suppress the hypothalamo-pituitary-gonadal axis<sup>15</sup> and produce inappropriate bone age

advance<sup>3</sup>; such high doses of oxandrolone induce puberty. We have shown that in low dose, short duration courses a sustained growth spurt is induced without virilisation. We believe oxandrolone is a useful treatment for boys with constitutional delay of growth and puberty when psychological problems associated with short stature predominate and when final height prognosis is towards the lower limit of normal; circumstances where it is imperative that no loss of height potential results from treatment. In view of the extensive experience with oxandrolone in North America, and more recently in the United Kingdom, we believe it would be of value if such a useful therapeutic modality were to be licenced for prescription in the United Kingdom.

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