A double blind, placebo controlled study of the effects of low dose testosterone undecanoate on the growth of small for age, prepubertal boys

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Abstract

Objective—To assess whether very low doses of testosterone can accelerate growth without an undue advance in bone age in prepubertal boys with constitutional delay of growth.

Subjects—23 prepubertal boys aged 11–14 years with height at or below the third centile for chronological age.

Design—Randomised, double blind trial comparing oral testosterone undecanoate 20 mg once daily versus placebo for six months. The 18 months' observation period of each subject comprised a six month pre-treatment period, followed by a six month treatment (testosterone undecanoate or placebo) period, and a six month period after termination of treatment.

Outcome measures—At intervals of six months standing and sitting height were measured. Bone age, pubertal stage, weight, and lean body mass were also determined. Growth hormone, luteinising hormone, and follicle stimulating hormone secretion and testosterone concentration were measured before, after, and six months after treatment.

Results—Boys taking testosterone undecanoate ($n=11$) showed a significantly greater height velocity (mean (SEM) 5.84 (0.53) cm/year) and sitting height velocity (3.54 (0.57) cm/year) during treatment than the placebo treated boys ($n=12$, height velocity=3.38 (0.22) cm/year, sitting height velocity=1.58 (0.19) cm/year. There were no significant differences between the groups regarding changes in growth hormone, gonadotrophins, testosterone, or dihydrotestosterone concentrations. Bone age was not advanced significantly more rapidly in either group.

Conclusions—There is accelerated gain in height during six months of treatment with low dose testosterone undecanoate, without a significantly greater rise in bone age compared with controls. Testosterone undecanoate is a safe, well tolerated, and effective treatment in the management of constitutional delay of growth.

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remains the most common reason for short stature in boys presenting to endocrine clinics. When such growth delay is accompanied by significant psychosocial impairment and/or educational difficulties, androgen or anabolic steroid treatment has been used to induce a rapid growth spurt. Methyltestosterone, oxandrolone, or fluoxymesterone for six months to several years have been used.¹ Retrospectively, all these agents improved growth velocity immediately but there was disagreement over whether final height was increased, decreased, or unchanged. More recent trials with low doses of the anabolic steroid oxandrolone² or testosterone oenanthate³ for only three months suggested that both were effective in promoting short term growth without unduly accelerating bone growth or compromising predicted final height. In addition, oxandrolone seemed to be able to sustain growth acceleration during the three months after discontinuation of treatment. This, however, was only observed in early pubertal boys and not in prepubertal boys with testes volumes <4 ml.⁴ This discrepancy may be explained by the fact that oxandrolone augments pituitary growth hormone secretion through a priming effect on the somatotrophs in the pubertal boy whereas in the prepubertal boy this is only observed with testosterone oenanthate treatment.⁵

The aim of the study was to assess whether very low doses of testosterone, as oral testosterone undecanoate 20 mg once daily, could accelerate growth velocity without an undue advance in bone age in boys suffering from constitutional delay of growth. The effects of such treatment on growth hormone and gonadotrophin secretion and testosterone concentration were also monitored.

Subjects and methods

Twenty three otherwise healthy prepubertal boys with height at or below the third centile for chronological age^{6,7} with chronological age between 11.0 and 14.0 years and bone age over 8.0 years were studied. Recruitment was from paediatric endocrinology clinics in Edinburgh ($n=17$) and Cardiff ($n=6$). These clinics receive referrals from a wide area of the east of Scotland and Wales. After blocked randomisation, using two blocks of 12, each boy was randomly allocated to receive either two capsules of testosterone undecanoate (Organon Laboratories, Cambridge) 10 mg daily orally for six months or identical placebo capsules. All subjects were observed for a total of 18 months, including six months before and

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Although constitutional growth delay is considered to be a 'normal growth variant, it

six months after treatment. Ethical permission for the study was granted by the paediatric/reproductive medicine ethics of medical research subcommittee of the Lothian Health Board and the child health ethics committee of the South Glamorgan Health Authority. Informed written consent was obtained from each boy's parent(s) after explanation of the procedures involved and provision of printed information. It was noted on the consent form that each child himself had freely consented to participate, and that he and his parent(s) were informed of their right to withdraw. The randomisation code for each patient was broken at the end of the 18 months study period so that further treatment, if any, could be considered.

At screening, a full history and examination for each subject was carried out to ensure that no treatable systemic illness, including endocrinopathy, was present. At intervals of six months height (including sitting height), weight, pubertal stage including axillary and pubic hair stages and testicular volume,⁸ two site skinfold thicknesses (triceps and subscapular), heart rate, and blood pressure were measured. Height and sitting height were measured with a Holtain stadiometer. Standing height to the last completed millimetre was taken with each boy in his bare feet, heels and back in contact with the wall, head held in the Frankfort plane. Subischial leg length was calculated by subtracting sitting height from standing height. Testicular volume was measured by comparison with a Prader orchidometer^{9 10} and skinfold thickness with Holtain calipers. Only prepubertal boys, defined as having a testicular volume of less than 4 ml¹¹ were eligible to enter the study. Lean body mass was calculated from body weight and skinfold thicknesses using the equations of Parizkova.¹² Radiography of the left hand and wrist with calculation of bone age was carried out at intervals of six months.¹³

At onset and completion of treatment, full blood indices (Coulter S⁺IV analyser) and biochemical values (Monarch centrifugal, Beckman and Discrete analysers) were measured. At onset of treatment plasma testosterone concentration was measured immediately before and at half hourly intervals for eight hours after the first dose of testosterone undecanoate or placebo. A single morning testosterone concentration was measured after cessation of treatment and six months thereafter. Each subject underwent three sessions of nocturnal blood sampling during which blood samples were withdrawn at 20 minute intervals. Growth hormone, luteinising hormone, and follicle stimulating hormone (FSH) concentrations were then measured for the samples taken during an eight hour period starting one hour after the recorded time of sleep onset. The next morning a 0.25 µg/kg gonadotrophin releasing hormone (GnRH) stimulation test was carried out, and the greatest rise in luteinising hormone and FSH during the following hour recorded. These overnight sessions were carried out shortly before the start, shortly after, and six months after cessation of treatment.

Serum growth hormone was measured using an immunoradiometric assay, calibrated in terms of growth hormone international standard 80/505. The assay employed ¹²⁵I-labelled mouse antigrowth hormone monoclonal antibody (from NETRIA, St Bartholemew's Hospital, London) and polyclonal antigrowth hormone antiserum (SAPU, Carluke) linked to insoluble magnetisable Dynospheres (Dyno Particles AS, Lillestrom, Norway). Internal quality control samples were included (between-batch coefficient of variation <8.5% from 2.2–49 mU/l of growth hormone), and performance in the UK national external quality assessment scheme for growth hormone was also satisfactory.

The gonadotrophin assays were performed using Delfia kits (Pharmacia Wallac, Turku, Finland). Fifty microlitres of samples were assayed in duplicate. The within-assay coefficients of variation based on 30 consecutive duplicates of quality controlled pooled plasma samples were 9.1%, 6.3%, and 7.1% for mean hormonal concentrations of 0.24, 0.48, and 0.96 U/l respectively. The average between-assay coefficients of variation were 7.5%. The mean detection limit of the assay was 0.04 U/l.

Statistical analysis using Student's *t* test was performed with Microsoft Statworks.

Results

No subject was withdrawn from the study due to non-compliance (evidenced on direct inquiry or by leftover capsule counts) or side effects. It did not prove possible to collect full data on heart rate, blood pressure, skinfold thickness, bone age, and blood sampling for six of the subjects. Measurements of growth on all 23 subjects were used to calculate velocities of their change during three six month periods: before treatment, during treatment, and after treatment. Growth velocities were

Table 1 Growth parameters of study groups, active and placebo, at each assessment

	Screening	Before treatment	After treatment	Six months after treatment
<i>n</i> =23				
Height (cm)				
Active	129.6 (0.6)	131.4 (0.7)	134.5 (0.5)	137.2 (0.6)
Placebo	130.1 (1.8)	132.2 (1.6)	134.3 (1.5)	136.3 (1.6)
Sitting height (cm)				
Active	67.4 (0.8)	68.3 (0.9)	70.2 (0.9)	71.4 (0.7)
Placebo	69.1 (0.9)	70.1 (0.8)	71.1 (0.8)	71.7 (0.9)
SILL (cm)				
Active	62.2 (0.7)	63.1 (0.9)	64.3 (0.9)	66.1 (1.0)
Placebo	61.0 (1.2)	62.1 (1.1)	63.2 (1.0)	64.7 (1.0)
Weight (kg)				
Active	26.4 (1.0)	27.2 (1.3)	29.1 (1.3)	30.9 (1.5)
Placebo	27.2 (1.3)	28.4 (1.0)	30.3 (1.1)	31.2 (1.2)
Mean testicular volume (ml)				
Active	2.1 (0.1)	2.2 (0.1)	3.1 (0.2)	4.3 (0.2)
Placebo	2.0 (0.1)	2.8 (0.3)	4.4 (0.3)	5.4 (0.5)
Axillary hair stage				
Active	1 (0)	1 (0)	1 (0)	1.5 (0.2)
Placebo	1 (0)	1 (0)	1.2 (0.1)	1.3 (0.1)
Pubic hair stage				
Active	1 (0)	1 (0)	1 (0)	1 (0)
Placebo	1 (0)	1 (0)	1 (0)	1 (0)
<i>n</i> =17				
Lean body mass (kg)				
Active	22.2 (0.8)	22.7 (1.1)	23.9 (1.0)	24.9 (1.0)
Placebo	23.0 (0.8)	23.5 (0.7)	24.5 (0.4)	25.2 (0.5)
Bone age (years)				
Active	10.2 (0.4)	11.0 (0.4)	11.5 (0.4)	12.0 (0.4)
Placebo	10.2 (0.7)	11.0 (0.6)	11.2 (0.5)	11.7 (0.5)

SILL=subischial leg length.

Table 2 Growth velocities for each treatment group, active and placebo, during each stage of the study

	Before treatment	During treatment	During six months after treatment stopped	During 12 months after treatment started
<i>n</i> =23				
Height velocity (cm/year)				
Active	3.18 (0.29)	5.84 (0.53)	5.60 (0.60)	5.71 (0.35)
Placebo	3.31 (0.41)	3.38 (0.22)	4.62 (0.49)	3.94 (0.26)
		* <i>p</i> =0.001		* <i>p</i> =0.001
Sitting height velocity (cm/year)				
Active	1.61 (0.22)	3.54 (0.57)	2.61 (0.49)	3.00 (0.35)
Placebo	1.62 (0.23)	1.58 (0.19)	1.38 (0.34)	1.53 (0.20)
		* <i>p</i> =0.003	* <i>p</i> =0.048	* <i>p</i> =0.001
<i>n</i> =17				
Lean body mass velocity (kg/year)				
Active	0.78 (0.68)	3.36 (0.44)	2.12 (0.56)	2.16 (0.36)
Placebo	0.74 (0.89)	3.00 (1.34)	1.74 (0.67)	1.82 (0.47)
Bone age velocity (year/year)				
Active	1.62 (0.4)	0.84 (0.25)	1.16 (0.27)	0.99 (0.22)
Placebo	1.84 (0.54)	0.51 (0.34)	1.15 (0.26)	0.77 (0.21)

*Significance, Student's *t* test, active *v* placebo.

also calculated for the 12 month period after the start of treatment.

Measures of growth parameters for each group at each stage of the study are shown in table 1. Mean (SEM) height velocity (5.84 (0.53) *v* 3.38 (0.22) cm/year, *p*=0.001, Student's *t* test) and sitting height velocity (3.54 (0.57) *v* 1.58 (0.19) cm/year, *p*=0.003) were significantly greater in the boys on active testosterone during the six months on treatment (fig 1 and table 2). When growth velocities were calculated for the full year after the start of treatment, the differences between the groups were still significant (height velocity: 5.71 (0.35) *v* 3.94 (0.26) cm/year, *p*=0.001; sitting height velocity: 3.00 (0.35) *v* 1.53 (0.20) cm/year, *p*=0.001). Bone age velocity was not significantly higher in the testosterone undecanoate treated group during (0.84 (0.25) *v* 0.51 (0.34) year/year) or after (1.16 (0.27) *v* 1.15 (0.26) year/year) treatment. There were no significant changes in vital signs or in haematological or biochemical parameters

Figure 1 Mean (SEM) height velocity (A) and sitting height velocity for each treatment group for each study period; **p*=0.05, ***p*=0.003, ****p*=0.001, Student's *t* test, active *v* placebo. **Figure 2** Mean (SEM) testosterone concentrations in treated group after ingestion of first 20 mg dose of testosterone undecanoate (*n*=9) and in placebo group (*n*=8).

during treatment. The testosterone absorption studies of the treated group showed a peak concentration of 16.0 (2.5) nmol/l, reached at 2.9 (0.6) hours after ingestion of the first capsules (fig 2).

A summary of mean and maximum nocturnal growth hormone, luteinising hormone, and FSH concentrations, response to GnRH and early morning testosterone and dihydrotestosterone concentrations during the study are shown in table 3. There were no significant differences between the testosterone undecanoate treated and placebo groups at any stage of the study as regards physiological growth hormone, luteinising hormone, or FSH secretion overnight, GnRH stimulated gonadotrophin rises or early morning testosterone or dihydrotestosterone concentrations.

Discussion

Short stature can be emotionally disabling and restrain the full realisation of a child's physical and intellectual potential.^{14 15} The efficacy of anabolic or sex steroids in promoting short term growth and increasing final height is as yet unproved. Carefully designed, controlled, prospective trials to determine the optimum regimen for growth acceleration are of great potential therapeutic benefit to many children.¹⁶ This study was designed to assess if low dose short term treatment with an orally active androgen can fulfil the therapeutic goal of promoting and sustaining skeletal growth while minimising epiphyseal maturation.

There are disadvantages associated with any relatively short term study of growth. In particular, with regard to studies around the time of puberty, it has been suggested that the evaluation of pubertal growth in pathological situations, and even physically physiological situations such as constitutional delay, should be performed using total pubertal height gain rather than peak height velocity or growth rate which are calculated after a follow up of shorter periods. In general, peak height velocity and/or growth rate are used because most studies are performed and completed before final height has been reached. We could not assess total pubertal height gain because each subject was recruited on the understanding that further or other growth promoting treatment could be instigated on completion of the 18 month assessment period. In addition,

Table 3 Plasma hormone concentrations for each treatment group, active and placebo, at each stage of the study (n=17)

	Before treatment	After treatment	During six months after treatment stopped
Growth hormone (mean overnight) (mU/l)			
Active	7.44 (1.54)	7.11 (0.70)	6.92 (0.98)
Placebo	6.66 (1.37)	8.32 (1.58)	7.22 (1.31)
Growth hormone (maximum) (mU/l)			
Active	25.63 (3.97)	28.61 (3.48)	27.29 (5.33)
Placebo	28.41 (6.56)	37.58 (7.72)	27.10 (5.28)
Luteinising hormone (mean overnight) (U/l)			
Active	0.51 (0.13)	1.76 (0.61)	2.34 (0.76)
Placebo	0.76 (0.29)	3.71 (1.59)	2.17 (0.41)
Luteinising hormone (maximum) (U/l)			
Active	2.21 (0.66)	3.96 (1.19)	4.29 (1.40)
Placebo	2.31 (0.56)	6.50 (2.41)	4.87 (0.96)
GnRH luteinising hormone rise (U/l)			
Active	3.16 (0.75)	8.70 (2.53)	7.20 (2.34)
Placebo	3.94 (1.20)	13.85 (5.58)	7.71 (1.02)
FSH (mean overnight) (U/l)			
Active	0.48 (0.05)	0.93 (0.15)	1.38 (0.25)
Placebo	0.55 (0.11)	0.68 (0.12)	0.80 (0.16)
FSH (maximum) (U/l)			
Active	0.79 (0.08)	1.65 (0.33)	1.99 (0.26)
Placebo	0.94 (0.18)	1.19 (0.15)	1.48 (0.31)
GnRH FSH rise (U/l)			
Active	1.91 (0.74)	1.71 (0.19)	1.30 (0.32)
Placebo	1.84 (0.48)	1.69 (0.28)	1.63 (0.28)
Testosterone (am) (nmol/l)			
Active	0.55 (0.06)	0.35 (0.14)	0.77 (0.27)
Placebo	0.50 (0.15)	0.36 (0.10)	0.68 (0.19)

GnRH=gonadotrophin hormone releasing hormone.

the object of the study was to assess the growth promoting effects of low dose testosterone undecanoate during and for a six month period after treatment, as the effect in this subgroup of boys, who often present with psychosocial difficulties, would require a fairly rapid effect. In cases of constitutional delay of growth and/or puberty, treatment is not started with an expectation of increased final height. In many cases the latter is unlikely to be compromised without treatment. Treatment offers patients the chance to 'catch up' with their peers' growth spurt. Our calculated results and comparisons deliberately focus on the period of the study only. Speculation on final adult height may be unnecessary for the reasons discussed above. Furthermore, the methods used to calculate a predicted final adult height are dogged with difficulties, particularly around the time of puberty. Final height predictions are less accurate in patients showing marked deviations from the range of physiological variations in height or marked differences between bone age and chronological age. All depend on bone age estimation, which includes errors inherent to reading x ray films and the characteristics of control (in this case placebo treated) children.

The choice of treatment for constitutional delay of growth and/or puberty will depend on a number of factors,¹⁷ including compliance by the patient and dependable absorption of the preparation. Testosterone undecanoate capsules are small and easily swallowed. In this and previous studies absorption has produced adequate testosterone concentrations within short periods, mimicking the diurnal pattern of physiological testosterone secretion in puberty when the preparation is taken with food in the morning.¹⁸⁻²⁰ In studies of boys in early puberty the drug has been administered in higher dose in the evening.²¹

The accelerated gain in height (in particular sitting height) during the six months of

treatment, without a significantly enhanced increase in bone age, is an encouraging finding which suggests that even at this low dose testosterone undecanoate taken orally can accelerate height gain and give a much needed psychological advantage to boys in this situation.

Further work is needed to determine the optimum length of treatment. Longer periods of observation would be required to assess the effect on final adult height. In this group of boys, however, final adult height is not the primary concern. As all cases of growth delay have significant bone age retardation, they will usually attain a reasonable adult height without intervention. More often it is the immediate future that concerns these subjects, so that a reasonably rapid acceleration of height gain in the short term can be seen as a positive outcome, provided that it is not accompanied by an excessive acceleration of skeletal maturity. Our results show that testosterone undecanoate is a safe, well tolerated, and effective treatment in the management of constitutional delay of growth.

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