

Treatment of hypogonadal adolescent boys with long acting subcutaneous testosterone pellets

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Abstract

Aims—Long acting subcutaneous testosterone pellets are of proved efficacy for the treatment of hypogonadal men, but have not been reported as a treatment modality in adolescent boys. **Pharmacodynamic studies** of subcutaneous testosterone release have shown prolonged normalisation of testosterone levels for at least four months. **Administration of a long acting, safe, effective, and convenient form of treatment is desirable when life-long treatment is indicated.**

Patients and methods—Eighteen boys (aged 13.9–17.5 years at the start of treatment)—seven with primary hypogonadism, nine with secondary hypogonadism, and two boys being treated with testosterone for tall stature—were given testosterone pellets (8–10 mg/kg) every six months for 18 months. Height, weight, pubertal status, and psychosocial parameters were assessed and follicle stimulating hormone, luteinising hormone, testosterone, prolactin, and lipids were measured at 0, 1, 3, 6, 12, and 18 months. Bone age was measured at 0 and 12 months.

Results—In all boys growth velocity continued appropriately for bone age. Puberty continued to progress in all boys and in two boys the amount of virilisation exceeded that seen with previous treatment with intramuscular testosterone. After testosterone administration, follicle stimulating hormone and luteinising hormone suppressed incompletely in the boys with primary hypogonadism. Serum testosterone ranged from 4.3 to 26.7 nmol/l at three months to less than 10 nmol/l at six months after implantation. Prolactin and lipid levels were normal throughout the study. By report, there was an improvement in mood and emotional wellbeing. No pellet extrusions occurred in a total of 156 pellet insertions.

Conclusions—All boys preferred this mode of testosterone administration to intramuscular injections. Long acting subcutaneous testosterone pellets are safe, efficacious, well tolerated, and convenient, and result in normal physical growth and improved psychological outlook in adolescent hypogonadal boys.

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Long acting subcutaneous testosterone pellets are of proved efficacy as a form of maintenance treatment in hypogonadal men. The pharmacodynamics and pharmacokinetics of implanted pellets have been established.¹ Implanted pellets produce sustained constant testosterone release over five months, testosterone levels being measured within the normal adult male range during this time. Although the treatment modality has been shown to be safe, effective, and convenient as a form of treatment in men,^{2,3} no study of this form of replacement treatment has been reported in adolescent boys.

Administration of androgen to adolescent boys requires a consideration of growth potential, pubertal progress, and the establishment of psychosocial and sexual identity. Dosage must therefore be graduated to produce androgen levels which are consistent with normal linear growth and a normal rate of epiphyseal maturation.

Treatment regimens for androgen replacement in adolescence usually employ the initial use of low potency androgens by mouth,⁴ with the later addition of intermittent intramuscular testosterone. Treatment with testosterone undecanoate by mouth is reported as producing a marked variability in plasma levels between subjects, marked suppression of sex hormone binding globulin (SHBG), and a failure of suppression of gonadotrophins in hypergonadotrophic states.⁵

Administration of intramuscular testosterone is associated with marked peak-trough variations in plasma levels of testosterone over a two week period and with significant side effects of local pain at the injection site, fluid retention, and gynaecomastia. Despite these disadvantages it does produce satisfactory masculinisation.^{6,7}

Administration of long acting subcutaneous testosterone pellets in adolescent boys where lifelong treatment is indicated offers the potential advantage of efficacy, safety, and convenience. This study aims to establish the role of subcutaneous treatment in this group of patients.

Patients and methods

This study aimed to establish a dosage range of testosterone which would produce adequate masculinisation without undue advancement of bone age, to document changes in hormonal and lipid profiles during treatment, and to document side effects, possible complications, or disadvantages of the treatment.

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Table 1 Data for growth and pubertal status at start of treatment (0 months) and at 12 months in 15 boys treated with long acting subcutaneous testosterone pellets

Patient No:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0 months															
Age (years)	17.08	16.25	17.5	15.75	16.75	18.2	17.33	16.33	16.1	13.85	16.25	16.6	17.4	15.65	18
Height (cm)	166.2	160	184.7	170	160.9	163.2	169.1	176.8	189.5	166	170.6	149.5	190.4	163.7	148.8
Weight (kg)	49.95	44.45	72.4	64	62.45	52.35	60.7	94.85	81.6	53.9	60.7	42	76.1	41.05	41.95
Pubic hair	4	4	5	2	4	3	6	4	6	4	5	4	5	4	4
Penis length (cm)	9.5	8	11.5	8	8	9	11.5	8.5	14	8	10	8.5	14	12	14
12 months															
Height (cm)	169.1	168.5	187.2	174.3	163.4	160.5	170.5	177.8	189.7	172.2	171.9	151	191	167	149.5
Weight (kg)	52.1	53.9	70.45	67.95	61.8	59	62.5	92.5	86	54.6	63.3	41	76.5	46.25	41.1
Pubic hair	5	5	6	4	5	—	5	—	6	5	5	4	6	5	5
Penis length (cm)	10	11	14	13	10	—	12	11	14	10	12	8	15	11.5	14
Bone age (0 months)	15	13.5	16	15	15	15.5	15.5	16	17	13	14.5	15.25	15.5	14	17
Bone age (12 months)	15	14.5	17	16	16	—	17	17	—	14	15.5	16	17	16	—

Sixteen boys attending the Royal Children's Hospital Endocrine Clinic who required testosterone replacement treatment for hypogonadism and two tall boys using testosterone to hasten epiphyseal closure were recruited for the study. Informed consent was obtained from all boys and their parents for participation in the study. The boys ranged in age from 13.9 to 17.5 years at the start of the study. All the boys had previously received some other form of testosterone treatment before the start of this study.

Testosterone pellets were administered subcutaneously at a dose of 8–10 mg/kg at 0, 6, 12, and 18 months. Five millilitres of lignocaine were administered subcutaneously into the buttock, injection beginning at a site 3 cm below the apex of the iliac crest. A 0.5 cm incision was made and diffuse crystalline testosterone pellets were implanted using a trochar and cannula method. A single suture was made at the incision site and the wound was covered with an occlusive dressing. Clinical and biochemical assessments were made at 0, 1, 3, 6, 12, and 18 months.

CLINICAL EVALUATION

Height was measured with a Harpenden stadiometer at each visit. Testicular size was assessed using a Prader orchidometer. Penile size was measured using stretched penile length with the length centile determined from previously published data.⁸ Pubertal staging was recorded according to the method of Tanner. Body weight and the extent of any gynaecomastia present were noted. Subjective commentary by all patients on changes in mood, memory, confidence, tiredness, and school performance was made at each visit.

Bone age was determined before the start of the study and at the end of the first 12 months by a single observer using the method of Greulich and Pyle.

BIOCHEMICAL EVALUATION

Fasting blood samples were drawn at each visit for the estimation of serum follicle stimulating hormone, luteinising hormone, testosterone, prolactin, cholesterol, and triglycerides. Hormonal assays for follicle stimulating hormone, luteinising hormone, testosterone, and prolactin were performed at the Royal Children's Hospital, department of clinical biochemistry. Follicle stimulating hormone and luteinising hormone were measured by radioimmunoassay

with the Amersham Amerlex-N kit. Follicle stimulating hormone and luteinising hormone were expressed in international units per litre of World Health Organisation standards. Testosterone was measured by radioimmunoassay using an in-house method with the tracer supplied by Monash Medical Centre chemical pathology department and prolactin was measured by radioimmunoassay with a Bioclone kit method. Cholesterol and triglycerides were measured by an enzymatic colorimetric method using a commercial kit (monotest, GPO-PAP).

Results

The treatment groups consisted of seven boys with primary hypogonadism due to anorchia (four boys), Noonan's syndrome (one boy), Klinefelter's syndrome (one boy), and testicular irradiation (one boy); nine boys with secondary hypogonadism due to Kallman's syndrome (five boys), hypopituitarism (three boys), Langerhan's histiocytosis (one boy); and two boys who had been treated for tall stature with testosterone to hasten epiphyseal closure.

Of the 18 boys who started the study protocol, 16 completed the full 18 months of the study. The two tall boys completed only 12 months of the study, one because he did not wish for further intervention and the other because he feared that the subcutaneous testosterone was ineffective and elected to return to intramuscular testosterone. One boy, who was aged 16 at the start of the study and who was thought to have hypogonadotropic hypogonadism based on the absence of pubertal change and a non-responsive LHRH test with low gonadotrophin levels, subsequently proceeded through normal pubertal development during the testosterone treatment and was withdrawn from the study.

CLINICAL FEATURES

Table 1 summarises the clinical parameters. The effect of treatment on height velocity varied widely according to the primary disorder in each boy. The greatest height increment occurred in those with the lowest bone age at the start of treatment. Weight increased in all the boys, with the rate of change dependent on, and appropriate for, height velocity during the study period. Weight loss occurred only in the two obese boys.

Bone age at the start of the study ranged between 12 and 16.5 years with a median age

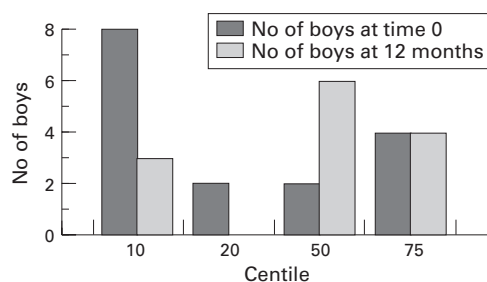


Figure 1 Changes in penile size with time.

of 14 years. Bone age increased in the first year of treatment in all boys whose bone age was less than 17 years at the start of the study. The maximum advance in bone age was 18 months and in most boys it was 12 months within the first year of study.

The change in penile size with time was greatest if the patients had previously taken only androgen by mouth. Of the three patients with a penile length less than the 10th centile at 12 months after the start of treatment, one had had previous gonadal irradiation for testicular relapse of leukaemia. Two boys who had previously used testosterone enanthate 250 mg every two weeks for more than one year before this study had a change in penile length from less than the 10th centile to more than the 50th centile during treatment with subcutaneous testosterone. At the start of treatment the penile length of nine patients was less than the 10th centile for age. At 12 months of treatment only three patients were less than the 10th centile (fig 1).

Pubic hair advanced from Tanner stage III to VI at the start of treatment to at least stage V in all patients after three months of treatment, except in the boy with previous gonadal irradiation. Testicular size did not change with time in any patient. Gynaecomastia was present in one patient (47XXY) at the start of treatment and was present in two boys at one month, but disappeared in all boys thereafter and did not recur throughout the remainder of the study.

Adverse events during the study were minimal, with one minor local infection at the site of pellet insertion and one episode of fibrosis at the site of pellet insertion in the patient whose pellet insertion was in the field of previous irradiation.

PSYCHOSOCIAL CHANGES

All boys preferred subcutaneous testosterone to intramuscular testosterone. No boy returned to intramuscular testosterone at the end of the study. After the first three months of the study, improvement was reported in various parameters of physical and emotional wellbeing, with improvements maintained over six months. One to three weeks before the next pellet insertion was due, 14 boys reported tiredness on each occasion.

PHARMACOLOGICAL CHANGES

Serial luteinising hormone and follicle stimulating hormone levels were only partly suppressed in the patients with primary (hypergo-

nadotropic) hypogonadism, with the lowest levels measured one month after pellet insertion. Mean follicle stimulating hormone concentrations decreased from 75 to 54 U/l by four weeks and returned to 65 U/l by three months. Mean luteinising hormone concentrations decreased from 50 to 30 U/l at one month, returning to 45 U/l by three months. Both remained markedly increased beyond levels seen in eugonadal males. The nadir of the mean follicle stimulating hormone values was higher than the nadir of the mean luteinising hormone values and remained markedly increased, as previously reported.¹ The basal range for follicle stimulating hormone was 40–104 mU/l and at three months 42–90 mU/l. The basal range for luteinising hormone was 28–120 mU/l and at three months 30–78 mU/l.

As expected, follicle stimulating hormone and luteinising hormone levels were low in boys with secondary (hypogonadotropic) hypogonadism and did not alter with testosterone treatment. By contrast, follicle stimulating hormone and luteinising hormone levels suppressed from 8 to 0.5 U/l, with a follicle stimulating hormone level of 10 U/l suppressing to 1 U/l by one month in the boy who was subsequently found to have had delayed puberty. These levels returned to baseline by three months of treatment.

Testosterone levels at baseline varied depending on the previous treatment administered to the boys. No patient entering this study had any administered testosterone less than two weeks before the study started. As the administered testosterone dose varied with the chronological and bone age of the boys, the testosterone levels reflected this variation. Figure 2 shows testosterone values over six months. At one month 16 boys had testosterone levels >10 nmol/l, whereas the two obese boys had levels <10 nmol/l. At three months the range was 4.3–26.7 nmol/l, with most values in the adult normal range of 10–30 nmol/l. At six months levels were returning to baseline and all but one were below the adult normal male range, the exception being the boy with pubertal delay.

All prolactin levels were within the normal range throughout the study period (133.7 ± 83.8 mU/l) for all boys, except those with panhypopituitarism where prolactin levels were low throughout the study.

Cholesterol levels were less than 5.5 mmol/l, the recommended upper limit of normal by the National Heart Foundation, Australia, throughout the study, with the exception of three samples of 5.6–5.9 mmol/l within the first six months of the study. By 12 months all levels were less than 5.5 mmol/l and remained normal throughout the remainder of the study period. Triglycerides were all <2.0 mmol/l throughout the 18 months.

Discussion

Growth velocity was appropriate for bone age in all boys and consistent with measured testosterone levels in the low to normal range for normal boys in mid to late puberty. This finding confirms the efficacy of subcutaneous

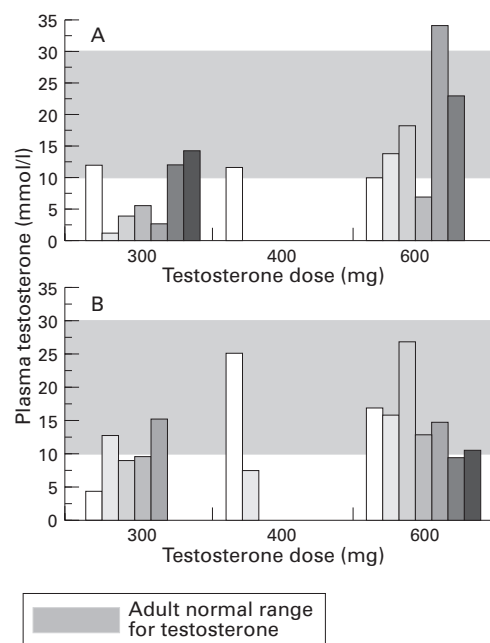


Figure 2 Variations in plasma testosterone concentrations with dosage at (A) one month and (B) three months.

testosterone in doses which produce pubertal plasma levels of testosterone, without major fluctuations, during prolonged periods.

Pubertal progress occurred appropriately in all boys, with a marked improvement in penile size with time so that all boys had a penile size within the normal adult range at the end of the study. Several of these boys had previously used intramuscular testosterone for long term replacement treatment before entry to this study. A further marked increase in penile size occurred after the initiation of subcutaneous testosterone, suggesting that the effective increased tissue availability of constant levels of testosterone may cause the growth of androgen sensitive tissues, perhaps by the induction of androgen receptors.

It is possible that a dislike of intramuscular injections may have led to poor compliance, but intramuscular treatment had been administered by local medical practitioners.

Previous studies have shown the efficacy of steady state testosterone levels in maintaining stable androgenic effects in castrate animals.⁹⁻¹⁰ Sex hormone binding globulin levels are maintained within the normal range in adults given subcutaneous testosterone compared with a 20% reduction in SHBG for intramuscular testosterone.¹⁻⁵ This is thought to reflect the more stable physiological testosterone levels obtained, without peaks and troughs of plasma levels or a marked portal-peripheral gradient,¹¹⁻¹² and may contribute to the increased clinical androgen effect.¹

Standardised protocols to examine psychosocial parameters were not undertaken as part of the study as the considerable alterations in perceived self confidence, energy, and mood were not anticipated at the start of the study.

A marked improvement was noted in psychosocial parameters, with decreased mood fluctuation consistent with constant testoster-

Key messages

- Continued normal progress of growth and pubertal status occurs with subcutaneous testosterone
- Prolonged stable physiological levels of testosterone are maintained for four to six months
- Bone age advance is commensurate with change in chronological age
- Psychological outlook and self image are reported to be improved
- Subcutaneous testosterone is safe, well tolerated, efficacious, and convenient

one release over the six months of each pellet usage. There have been similar reports of increased cheerfulness and relaxation in hypogonadal men receiving androgen replacement treatment.¹³⁻¹⁴ Independence from a therapist compared with the need for visits to a medical practitioner every two weeks for injections improved self confidence, energy, and mood. An improved self image with less attention being drawn to 'disability' minimises the feeling of a physical loss and perceived difference from other normal adolescents. This altered perception should allow an improved milieu for the development of sexuality and sex role identity during adolescence in these boys.

Physical parameters during subcutaneous testosterone treatment of continued normal virilisation, lack of fluid retention, lack of gynaecomastia, and minimisation of painful intervention by injections were all perceived advantages, again with less attention being drawn to a disability. No boy reported sexual activity at any time during the study, despite most boys reporting a regular frequency of erection and ejaculation.¹⁵ This differs considerably from reported sexual activity in the general population of 16-20 year olds and may reflect a poor sexual image in this study group, suggesting a need for further support to be offered for this group of boys.

The failure of even moderate suppression of gonadotrophins in this group of boys probably relates to the lower doses of testosterone used in a situation of hypergonadotrophic hypogonadism than that used in previous studies in adults where gonadotrophins did suppress further towards the normal range, but not completely into the normal range¹⁻⁵ in the case of follicle stimulating hormone, again supporting the role of inhibin in the non-steroidal feedback control of follicle stimulating hormone.¹⁶ The normalisation of lipid profiles and maintenance of normal lipid levels supports the concept of appropriate parenteral formulation of testosterone avoiding the potentially harmful effects on liver function of supra-physiological testosterone levels.¹⁷ The levels of testosterone returning to baseline by six months in this study was consistent with previously reported results using similar regimens.²

This study confirms the lack of side effects and the safety of the procedure of subcutane-

ous pellet implantation. The minimal disadvantage of a minor surgical procedure necessitating a degree of technical skill was far outweighed by the benefits of physical and psychosocial improvement and independence from a therapist.

Conclusions

Long acting subcutaneous testosterone pellets are safe, efficacious, well tolerated, and convenient, and result in normal physical growth and improved psychological outlook in adolescent hypogonadal boys. A controlled study would be of value to assess further the apparent psychological and emotional improvements seen in this study.

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