

# Monitoring Serum Testosterone Levels on Androgen Therapy with Long-Acting Testosterone Esters in the Prepubertal and Pubertal Age Groups

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Long-acting intramuscular testosterone esters at various doses using various protocols are suggested for the treatment of micropenis and/or delayed puberty of childhood. The objective of this study was to determine the duration of effective testosterone concentration and the optimum interval for the injections. Twenty cases were included in the study. Ten cases were in the prepubertal age with micropenis and the remaining 10 cases were in the pubertal age with constitutional delay of puberty. The prepubertal and pubertal group respectively received 50 mg or 100 mg of long-acting testosterone esters (sustanon) intramuscularly once a month. Blood samples for plasma testosterone levels were taken at the onset and on the 7th, 15th and 30th days of treatment. In the prepubertal group the mean 7th, 15th and 30th day plasma testosterone levels were found to be significantly higher than the mean level before treatment. In the pubertal age group, the desired effective plasma testosterone level was reached on the 7th day but we observed that the level decreased significantly on the 15th day and that the effect vanished on the 30th day. Intramuscular treatment with sustanon 100 mg once a month could not sustain an effective level on the 15th day in 85.7 % of the pubertal age group. Intramuscular treatment with sustanon 50 mg once a month is sufficient to improve penile length but causes a marked increase in the serum testosterone levels on the 7th day of treatment and sustanon 25 mg once a month may therefore be preferred in the prepubertal group. In the pubertal age we conclude that intramuscular sustanon 100 mg treatment should be given every 15 days.

**Key words:** testosterone therapy, micropenis, delayed puberty

## Introduction

Intramuscular administration of long-acting testosterone esters is the most commonly used treatment for male hypogonadism (1-3). There are various established guidelines in adulthood for male and female sex hormone replacement treatment, whereas great variability with no consensus exists for the management of children and adolescents. Testosterone has been widely used for the management of constitutional delay of puberty (4,5) and micropenis (6-9) in the pediatric age group. The most important issue is whether the child will have sufficient penile growth to allow

sexual function as an adult. In boys with constitutional delay of growth and puberty (CDGP), especially when there are significant psychosocial consequences of the delayed sexual development, testosterone administration can induce sexual development and enhance the growth-promoting effect of growth hormone.

The dose of sex hormone should not exceed that needed to allow physical development which is peer group appropriate. The general goal of testosterone therapy is to achieve physiological levels of testosterone with minimum adverse effects. Long-acting intramuscular testosterone preparations are administered at different doses using various protocols (1,2,10,11). In general, depot testosterone is injected at 14-day intervals in adult hypogonadal men (1-3,10,12) and at 30-day intervals in the pediatric age group for micropenis or to achieve pubertal induction (4,5,9,13). Measurement of serum testosterone levels is the most

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cost-effective way of monitoring testosterone replacement treatment. The main issue is to determine the method which will establish an effective plasma testosterone concentration.

In this study, our aim was to determine the duration of effective testosterone concentration after the intramuscular injection of long-acting depot testosterone in the prepubertal and pubertal age groups and the injection intervals that should be used.

### Patients and Methods

**Patients:** Twenty boys who presented at our outpatient clinic for isolated micropenis or constitutional delay of growth and puberty were included in this study. Ten of these patients were diagnosed as having micropenis and were in the prepubertal age group (mean age  $6.0 \pm 2.4$  years). Micropenis is defined as a morphologically normal penis, with a penile urethra, the stretched length of which, measured along the dorsal surface from the pubis to the tip of the glands, is more than  $-2.5$  SD below the mean value for the age or stage of sexual development (14,15). The normal standards were utilized for our clinical discrimination of micropenis (16). In the micropenis cases there were no other virilisation defects or dysmorphic findings and the testosterone response to hCG stimulation and gonadotropin response to LH-RH stimulation were normal. The remaining 10 cases were diagnosed as constitutional delay of growth and puberty (CDGP) (mean age  $14.2 \pm 1.1$  years). The diagnosis of CDGP was made on clinical grounds when no pubertal signs were present (testicular volume  $< 4$  ml) at a chronological age of 13 years, and the bone age was delayed more than  $11/2$  year (17). The testicular volume of the patients was assessed using the Prader orchidometer (18) and the data evaluated according to the criteria of Styne (19). The height standard deviation of the patients was calculated as  $-2.01 \pm 0.5$  SD, while the mean bone age was  $12.4 \pm 0.8$  years. The testosterone response to hCG stimulation was within normal limits (D testosterone  $^3 100$  ng/dl). LH-RH-stimulated gonadotropin values (LH and FSH) were low for the chronological age but normal for the bone age.

**Study Design:** Ten boys who were diagnosed as having micropenis were administered sustanon 50 mg (testosterone propionate, phenylpropionate and isocaproate) monthly. The remaining 10 patients

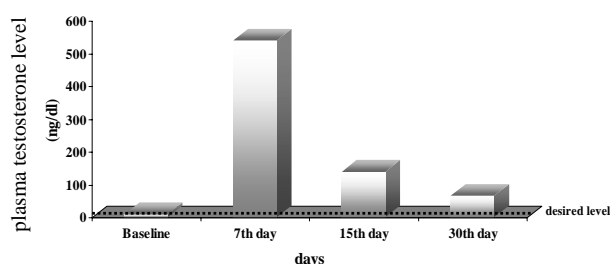
with delayed puberty were administered intramuscular sustanon 100 mg monthly for pubertal induction. Baseline plasma testosterone measurements of all patients were obtained before the injections and on the 7th, 15th and 30th days of treatment. All blood samples were taken between 8.00 and 9.00 a.m. Plasma testosterone levels were measured with RIA (radioimmunoassay) kits. The desired plasma testosterone level was accepted to be 14.4 ng/dl (0.49 nmol/L) in the prepubertal and 288 ng/dl (9.98 nmol/L) in the pubertal age group (20).

**Statistical analyses:** Comparison of the baseline plasma testosterone level with the levels on the 7th, 15th and 30th days of treatment were performed with Wilcoxon test. The percentage of the cases reaching and maintaining the desired testosterone level were determined. These comparisons were evaluated separately for the micropenis and constitutional delay of puberty patients.

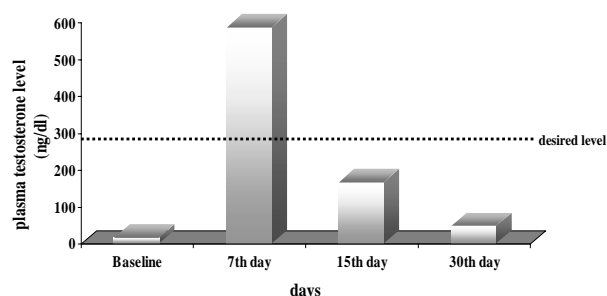
### Results

The mean baseline plasma testosterone level of the patients with micropenis in the prepubertal age group was  $10.14 \pm 0.37$  ng/dl ( $0.35 \pm 0.01$  nmol/L). The plasma testosterone levels after sustanon 50 mg application were  $539.70 \pm 252.78$  ng/dl ( $18.71 \pm 8.76$  nmol/L) on the 7th day,  $139.85 \pm 60.94$  ng/dl ( $4.84 \pm 2.11$  nmol/L) on the 15th day, and  $66.85 \pm 36.15$  ng/dl ( $2.31 \pm 1.25$  nmol/L) on the 30th day (Table 1). When the 7th, 15th, and 30th day mean testosterone levels were compared with the baseline levels, all were found to be significantly high ( $p < 0.01$ ). Moreover, in the prepubertal age group plasma testosterone levels were higher than the desired level even on the 30th day (Figure 1).

In the pubertal age group, the mean baseline plasma testosterone level before treatment was  $18.01 \pm 9.34$  ng/dl ( $0.62 \pm 0.32$  nmol/L) and the plasma testosterone levels after treatment were  $586.00 \pm 303.01$  ng/dl ( $20.31 \pm 10.50$  nmol/L) on the 7th day,  $156.71 \pm 93.59$  ng/dl ( $5.43 \pm 3.24$  nmol/L) on the 15th day and  $54.02 \pm 25.15$  ng/dl ( $1.87 \pm 0.87$  nmol/L) on the 30th day (Table 1). According to our results monthly testosterone injections could not maintain the desired plasma testosterone levels after the 15th day following the injection in the pubertal age group. The effective testosterone level decreased significantly by the 15th day ( $p < 0.01$ ) and the effect vanished on the 30th day in this age group (Figure 2).



**Figure 1.** The change over time of plasma testosterone levels following intramuscular depot testosterone injection in prepubertal patients with micropenis



**Figure 2.** The change over time of plasma testosterone levels following intramuscular depot testosterone injection in pubertal patients with constitutional pubertal delay

When sustanon 50 mg once a month was continued for four months the penile length of all cases in the prepubertal group reached to the normal ranges for age. Administration of sustanon 100 mg once a month for four months in the CDGP group lead to pubertal induction. As a result the testis volume was 4 ml or over in all cases. We continue to follow-up these cases for their pubertal prog-reSSION.

## Discussion

Our study showed that monthly intramuscular sustanon injections is sufficient for the treatment of micropenis in the prepubertal age group when used at a dose of 50 mg. On the other hand, although a dose of 100 mg sustanon was used for pubertal induction in the pubertal age group it was observed that the efficacy did not last as long as four weeks in the great majority of patients (85.7%).

Irrespective of the underlying cause, a short course of testosterone should be tried on all patients with micropenis (21,22). The treatment of micropenis should be started as early as possible. Best outcomes are achieved when testosterone therapy has been administered in the first few months of life. Administration of 25mg testosterone enanthate per month for 3 months is recommended after a

positive hCG test in infancy (6,9,23). In another study, all patients with micropenis received either one or two courses of 25 to 50 mg of testosterone enanthate in oil monthly for three or four doses in infancy or childhood to induce phallic growth into the normal range for age (6,7). The side effects of this short course of testosterone therapy are minimal and include temporary accelerated growth velocity and bone age (24). In our study in which sustanon 50 mg was administered for the treatment of micropenis, plasma testosterone levels reached very high levels on the 7th day of therapy. As this high testosterone level could have adverse affects, these patients should be observed and evaluated in order to determine progression of their height and bone ages. Very high testosterone levels seen even with small doses like 50 mg leads us to think that smaller doses could be sufficient. This point needs to be illuminated with further studies.

Patients with CDGP have delayed development and their endocrine function is normal for the stage of physiological development but not for the chronological age. Many of these boys are distressed about their shortness and immature appearance. Interest in the use of testosterone to initiate the adolescent growth spurt has resulted in a variety of treatment regimens (25,26). Kelly BP et al used a single 3-month course of testosterone enanthate 125 mg per month by intramuscular injection for constitutional delay in growth and adolescence. They showed that there was no significant difference in the final height between boys treated with testosterone enanthate and those who had no treatment (27). Low dose testosterone therapy (100mg/month intramuscularly) for four to six months can be offered, which can make the patients look more mature and induce pubertal progression (28). Our results showed that testosterone levels higher than the desired levels are obtained at the 7th day of treatment with an injection of sustanon 100 mg in pubertal and with 50 mg in prepubertal patients. We conclude that sustanon 100 mg is sufficient for pubertal induction because all our patients had plasma testosterone levels higher than the desired level on the 7th day of treatment. However, we observed that this effective level decreased on the 15th day in 85,7 % of our patients. We thus suggest that when sustanon is given for pubertal induction plasma testosterone levels should be re-evaluated on the 15th day of therapy and the same medication given once every 15 days at half dose if

the plasma testosterone levels are found to be lower than the desired level.

In conclusion, the increase in penile length was adequate with the 50 mg sustanon treatment once a month in the prepubertal group but there was a marked increase in the serum testosterone levels on the 7th day of treatment and sustanon 25 mg once a month may therefore be preferred in this group. Although 100 mg sustanon once a month induces puberty the low serum testosterone levels 15 days after the injection in 85.7% of the cases suggest that this treatment will be inadequate for hypogonadotropic hypogonadism cases. The 15th day serum testosterone level is therefore important during the monitoring of pubertal age group treatment. Intramuscular treatment with sustanon 100 mg once every two weeks appears to be a better form of therapy in most pubertal patients. The probable negative effect of the exaggerated hormone levels during the first week should be evaluated in both age groups but especially in the prepubertal group.

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