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EFFECT OF TESTOSTERONE ENANTHATE ON TESTIS SIZE

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ABSTRACT

We treated chronically 39 normal men with a depot androgen, testosterone enanthate (200 mg. intramuscularly), to assess its potential as a male contraceptive agent. Careful examination and quantification of testicular volume were done before, during and after several dose regimens of androgen therapy.

After 4 months of weekly or bimonthly treatment with testosterone enanthate testicular volume decreased by 19.0 plus or minus 2.1 and 16.5 plus or minus 3.4 per cent, respectively. Decrease in testicular volume was related directly to decrease in sperm count. A total of 17 subjects on either weekly or bimonthly injections failed to suppress sperm counts to less than 5 million per cc after 16 weeks; testicular volume was not significantly less than control at this time. Four to 12 weeks of additional weekly injections decreased sperm counts to less than 5 million per cc in 13 of the 17 patients and decreased testicular volume by 23.0 plus or minus 4.8 per cent. The 16 additional weeks of less frequent injections (every 3 or 4 weeks) resulted in an increase in testicular volume with a return to normal size after treatment was discontinued.

Since 1950 several investigators have determined that testosterone administration inhibits spermatogenesis.[1, 2] It was reported that while testosterone administration to oligospermic men initially suppressed spermatogenesis a significant number of these subjects experienced a marked increase in sperm counts after treatment was discontinued.[2-5] Testosterone rebound therapy presently is used widely in the treatment of oligospermic male patients. Based upon this evidence of reversible suppression of gonadotropin secretion and spermatogenesis, testosterone, either alone or in combination with progesterones, is being studied for use as a male contraceptive agent. Although no significant clinical side effects have been reported information on testis size is lacking. Recently, several investigators using either testosterone enanthate alone or testosterone enanthate plus medroxyprogesterone acetate have reported the attainment of considerable oligospermia and/or azoospermia with no change in testicular size.[6-10] Other investigators using testosterone have reported decreases in testicular size concomitant with decreasing sperm counts.[11, 12]

There is no information available concerning changes in testicular size either in patients with chronic anemia on androgen therapy or in normal male subjects using androgens as muscle builders, such as competitive athletes. We herein report data on testicular size in 39 normal men who received testosterone enanthate as an experimental male contraceptive agent.

MATERIALS AND METHODS

Volunteer subjects. A total of 53 male volunteers between 21 and 39 years old participated in the study. Each subject was informed of the nature of the study and all were believed to be free of systemic or psychiatric disease, were taking no medications known to influence reproductive function and had normal physical examinations. Before entry into the study each volunteer was screened for abnormalities in reproductive hormone values (luteinizing hormone, follicle-stimulating hormone, testosterone and estradiol), liver function tests, blood count, fasting blood sugar, lipids and electrolytes, and 3 serial semen analyses were performed. Only the 39 subjects completing the study were included in data analysis.

Protocol. The study was divided into 4 phases: 1) a control phase lasting 8 weeks, 2) a treatment phase I lasting ≧16 weeks, 3) a treatment phase II lasting ≧16 weeks and 4) a recovery period that lasted until all laboratory test results returned to normal. Upon entry into the first treatment phase the subjects were divided into 2 groups. Group A (17 subjects) received 200 mg. testosterone enanthate intramuscularly every week, while group B (22 subjects) received the same dose every 2 weeks. If a subject had a sperm count of <5 million per cc for 2 consecutive measurements by week 16 of treatment phase I then treatment phase II was begun. Those subjects in group B who had sperm counts >5 million per cc at 16 weeks were placed on weekly treatment for an additional 16 weeks or until the sperm counts met the aforementioned criteria for entry into treatment phase II. Some of the subjects in group A who did not meet the criteria for entry into phase II were continued on weekly treatment for an additional 1 to 4 weeks. All subjects failing to suppress sperm counts after the aforementioned regimen were placed in the recovery phase.

Upon entry into treatment phase II the patients were randomized and received 200 mg. testosterone enanthate either every 3 or every 4 weeks for 24 weeks.

Laboratory tests. Blood samples were obtained for luteinizing hormone, follicle-stimulating hormone, testosterone and estradiol[13-16] during treatment before each injection of testosterone enanthate. Semen analyses were performed on each subject every 2 weeks in each phase of treatment and recovery.

Physical examinations. A complete physical examination was done monthly and testicular size was measured carefully by 2 investigators using a Prader orchidometer, consisting of 2 series of graduated wooden oval forms varying in size from 1 to 25 cc. Each testis was examined independently and the mean value for the 2 testes is presented herein.

RESULTS

Testicular size is presented in absolute size, mean percentage changes and absolute changes (see table). Statistical significance was determined using paired t tests.

Twelve subjects on weekly testosterone treatment (group A, phase I) evidenced significant decrease in testicular size (18.8 ± 1.1 versus 23.1 ± 0.8 cc). The mean decrease in the weekly group (phase I) was 19.0 ± 2.1 per cent (change of 4.3 ± 0.7 cc, $p < 0.05$). Once subjects were switched to less frequent injections, either 3 or 4 weekly (phase II), testis size started to

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Testis size (plus or minus standard deviation)

	Control	Phase I	Phase IA	Phase II	Recovery (No.)
			Absolute size (cc)		
Weekly	23.1 ± 0.8	18.8 ± 1.1		20.6 ± 1.3	22.4 ± 1.0 (12)
Biweekly	19.5 ± 1.7	16.6 ± 1.3		16.9 ± 2.2	18.2 ± 2.0 (10)
Special	19.2 ± 1.4	17.8 ± 1.6	15.0 ± 1.1	15.4 ± 1.4	18.9 ± 1.6 (17)
			% changes		
Weekly		−19.0 ± 2.1		−12.3 ± 5	−5.4 ± 2.9 (12)
Biweekly		−16.5 ± 3.4		−15.7 ± 4.7	−7.1 ± 2.8 (10)
Special		−7.8 ± 3.5	−23.0 ± 4.8	−19.6 ± 5.1	−2.4 ± 3.8 (17)
			Absolute changes (cc)		
Weekly		−4.3 ± 0.7*		−2.9 ± 1.2	0.7 ± 0.8 (12)
Biweekly		−2.9 ± 0.5*		−2.5 ± 0.7	−1.2 ± 0.4 (10)
Special		−1.5 ± 0.8†	−4.2 ± 0.8*	−3.9 ± 1.1	−0.3 ± 0.6 (17)

* $p < 0.05$.
† Not significant.

increase (20.6 ± 1.3 cc) and returned to control measurements during the recovery period (22.4 ± 1.0 cc).

Ten subjects (group B) on biweekly testosterone enanthate treatment (phase I) also presented significant decreases in testicular size (16.6 ± 1.3 versus 19.5 ± 1.7 cc). The mean decrease in the biweekly group was 16.5 ± 3.4 per cent (change of −2.9 ± 0.5 cc, $p < 0.05$). Once subjects were switched to less frequent injections, either 3 or 4 weekly (phase II), testis size started to increase (16.9 ± 2.2 cc) and returned to close to control measurements during the recovery period (18.2 ± 2.0 cc).

Seventeen subjects (special) from either group A or B failed to suppress sperm counts to <5 million sperm per cc despite 16 weeks of testosterone enanthate treatment. These subjects evidenced a non-significant decrease in testicular size (17.8 ± 1.6 versus 19.2 ± 1.4 cc). The mean decrease in this group (phase I) was −7.8 ± 3.5 per cent (change of 1.5 ± 0.8 cc, not significant). These patients were placed on an additional 4 to 20 weeks of weekly administration (phase IA). When the additional treatment resulted in a significant suppression of sperm count testicular size also decreased significantly (15.0 ± 1.1 versus 19.2 ± 1.4 cc), with a mean decrease of −23.0 ± 4.8 per cent (change of 4.2 ± 0.8 cc, $p < 0.05$). Once these subjects were switched to less frequent injections, either 3 or 4 weekly, testis size started to increase (15.4 ± 1.4 cc), returning to close to control values during the recovery period (18.9 ± 1.6 cc).

Results from hormonal tests and semen analyses have been published previously.[17, 18] In the weekly group serum testosterone and estradiol increased approximately 60 per cent over control values; there was no significant increase in serum testosterone in the biweekly group. Luteinizing and follicle-stimulating hormones were depressed approximately 60 per cent below control values, returning to normal levels during the recovery phase. Sperm counts decreased to severe oligospermic (<5 million per cc) or azoospermic levels in most subjects (35 of 39), returning to basal levels in all subjects during the recovery phase.

DISCUSSION

In our group all subjects who suppressed sperm counts demonstrated a significant dose-dependent decrease in testicular size. The few subjects who did not suppress sperm counts to severe oligospermic levels were those with less evident decrease in testicular size. The observed decrease in testicular size after depot testosterone administration is presumed to be secondary to inhibition of luteinizing and follicle-stimulating hormones with secondary suppression of the germinal cells, which account for approximately 75 per cent of the mass of the adult testis. Since luteinizing and follicle-stimulating hormones are suppressed by the testosterone treatment it is unclear whether the decrease in spermatogenesis and testis size is the result of loss of follicle-stimulating hormone stimulation of the Sertoli cells or is owing to diminished luteinizing hormone stimulation of testosterone effect on the germinal elements. Data to support the primary role of luteinizing hormone suppression on decreased testis size come from the studies of Heller and associates, demonstrating reversal of inhibition of spermatogenesis in men treated with combined testosterone and human chorionic gonadotropin.[19]

The changes in testicular size were reversible completely once treatment was discontinued. Although only a few subjects were aware of these changes, and then only after questioning, assurance of reversibility was given. Our results are in agreement with those reported by Mauss and associates[11] and Reddy and Rao[12] who administered testosterone enanthate and testosterone propionate, respectively, for a prolonged interval to normal volunteers. These investigators also demonstrated decreased testicular size in their subjects. Recently, Cunningham and associates reported significant suppression of sperm count with no change in testicular size in 20 men who received testosterone enanthate for 42 weeks.[20] However, no information was given on the method of measuring testis size.

The reports of some investigators who used testosterone and medroxyprogesterone acetate and obtained significant levels of oligospermia or azoospermia without change in testis size indicate that a more objective method of measuring testis size is necessary, for example an orchidometer. Clinical observation may not be accurate; since most of the testicular mass is formed by the germinal cells it seems unlikely that severe oligospermia or azoospermia would occur without change in testicular size.

There have been reports of subjects receiving testosterone rebound therapy who have failed to increase sperm counts after treatment. This probably reflects an underlying disorder and such subjects would be expected to have a progressive decrease in sperm count and testis size.

Patients receiving androgen therapy for other disorders also can be expected to experience decreased testis size and this side effect should be explained carefully to avoid additional stress to patients with such disorders as chronic renal failure and bone marrow depression.

In summary, chronic administration of testosterone enanthate produces modest increases in serum testosterone and estradiol, and decreases in luteinizing and follicle-stimulating hormones, inhibiting spermatogenesis and decreasing testis size. All of these changes are reversible in normal subjects.

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