

COMPARISON OF THE EFFECTS OF HIGH DOSE TESTOSTERONE AND 19-NORTESTOSTERONE TO A REPLACEMENT DOSE OF TESTOSTERONE ON STRENGTH AND BODY COMPOSITION IN NORMAL MEN

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Summary—We examined the extent to which supraphysiological doses of androgen can modify body composition and strength in normally virilized men. In doubly blind tests, 30 healthy young men received testosterone enanthate (TE) or 19-nortestosterone decanoate (ND), at 100 mg/wk or 300 mg/wk for 6 weeks. The TE-100 mg/wk group served as replacement dose comparison, maintaining pretreatment serum testosterone levels, while keeping all subjects blinded to treatment, particularly through reduction in testicular volumes. Isokinetic strength measurements were made for the biceps brachii and quadriceps femoris muscle groups before treatment and 2–3 days after the 6th injection. Small improvements were noted in all groups but the changes were highly variable; a trend to greater and more consistent strength gain occurred in the TE-300 mg/wk group. There was no change in weight for TE-100 mg/wk but an average gain of 3 kg in each of the other groups. No changes in 4 skinfold thicknesses or in estimated percent body fat were observed. Of 15 circumferences, significant increases were observed only for men receiving TE-300 mg/wk (shoulders) and ND-300 mg/wk (shoulders and chest). The data suggest that high dose androgens increase body mass and may increase strength in normal men but, except for a consistent weight gain with greater than replacement doses, the detectable changes were highly variable and relatively small, especially in comparison to the significant alterations which were observed for other markers of androgen action.

INTRODUCTION

Early studies with castrated animals characterized the nitrogen retaining “anabolic” properties of androgens and led to the conclusion that these actions were responsible for the sexually dimorphic musculature in humans [1, 2]. Extrapolating from these replacement studies, eugonadal athletes have attempted to enhance already highly developed physiques and competitive sports performances with the self-administration of high doses of androgens [3]. Androgens with a high protein anabolic activity (on the basis of a preferential effect on the growth of castrated rat levator ani muscle over the effect on ventral

prostate growth) such as methandrostenolone and 19-nortestosterone (nandrolone) [4] are especially popular with athletes [5]. Body builders claim from anecdotal experience that these steroids increase muscle size without producing unwanted side effects, such as increased sebum production and reduction in sperm count; on the other hand, many strength athletes prefer testosterone preparations for the enhancement of their lifting performance and continue to use them even after they encounter side effects such as gynecomastia [6]. However, few studies have compared these androgens to testosterone to demonstrate which actions are enhanced in an anabolic steroid in normal men, and surprisingly, there are no studies which have examined the effect of greater than replacement doses of testosterone on muscular strength and size.

Two androgen esters with very different anabolic/androgenic indices, testosterone enanthate (TE) and 19-nortestosterone decanoate (ND) are frequently used in clinical practice and these

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two rank highest in popularity with athletes using parenteral preparations [5]. TE and ND have similar halftimes to elimination of about 1 week [7–9]; however, their metabolism to other biologically active compounds is different and this could be expected to modify their physiological activity. The 5α -reduction of 19-nortestosterone markedly reduces androgen receptor binding affinity [10, 11] which would imply a reduced action in tissues where intracellular 5α -reduction is important for the biological effect, such as in the accessory sex organs. TE is primarily aromatized to 17β -estradiol while ND is not [12] and this might differentially affect tissues where aromatization is important in the mediation of testosterone actions. Thus, there is a biochemical basis to expect differences in the properties of these two androgens.

We compared the effects of TE and ND at two doses, one which is close to a replacement dose of TE (i.e. which maintained normal morning levels of serum testosterone) and one which produced serum levels of testosterone approx. 3-fold higher than physiological levels, in normal men given the drugs for 6 weeks. The effects of body size and muscular strength were examined and contrasted with other better defined androgenic actions.

EXPERIMENTAL

Thirty healthy men, aged 27 ± 5 years (20–37 years) participated in this study. Two subjects were smokers (10 cigarettes/day) and were distributed to separate treatment groups. All subjects were physically active soldiers (9 regularly performed resistance exercise, 1 was a bicyclist, the other 20 subjects exercised by running). The men were on self-selected diets and they were encouraged not to change their training or diet during the study. Results of a glucose tolerance test on this group have been reported elsewhere [13].

The men were randomly assorted into 4 groups of 7–8 subjects per group and received weekly i.m. (gluteal site) injections of steroid for 6 weeks. Each subject received either TE (Delatestryl, E.R. Squibb & Sons Inc., Princeton, NJ), at 100 or 300 mg/wk, or ND (Deca-Durabolin, Organon Inc., West Orange, NJ), at 100 or 300 mg/wk. Subjects and investigators were blinded to the treatment until completion of the study.

Sampling and testing were performed before drug administration and in the week following

the 6th injection. In each of these two testing sessions two blood samples were collected on separate days between 08.00–10.00 h following a 10 h fast, two semen samples were obtained (each following a 48 h abstinence from sexual activity), body circumferences and skinfold measurements were obtained, and strength measurements were made for an upper (elbow) and a lower (knee) body joint.

Fifteen body circumference measurements were made [14], four skinfold thicknesses were measured [15], and percent body fat was estimated from skinfolds [15]. Isokinetic muscle strength was measured using a Cybex II dynamometer (Lumex Inc., Ronkonkoma, NY). Subjects were positioned according to standard testing procedures for elbow flexion and knee extension as outlined by the manufacturer. Maximum peak torque for each muscle tested was recorded from four maximum contractions at angular velocities of 60 and 240°/s. Right extremities were tested, except in one case, where a pre-existing right knee injury necessitated a left knee test; upper extremities were tested first.

Semen samples were submitted within 1 h of collection and analyzed according to standard procedures; fructose concentration was measured in the seminal plasma using a colorimetric assay. Testicular volumes were calculated from caliper measurements [16]. Serum aliquots were frozen at -70°C until the samples were assayed in duplicate by RIA for testosterone [17], estradiol- 17β and estrone (Nichols Laboratories, San Juan Capistrano, CA), LH, FSH and prolactin (Radioassay Systems Laboratories, Carson, CA), and sex hormone binding globulin (SHBG) (Farnos Diagnostica, Oulunsalo, Finland). Serum lipids and apolipoprotein A-1 were measured as described previously [17]. Randomly selected urine specimens were tested and no exogenous steroids other than those administered were detected [13].

A repeated measures analysis of variance (ANOVA) was used to compare differences between groups over time and paired *t* tests were used to compare baseline and treatment measurements within groups.

RESULTS

Body weight increased significantly with TE-300 mg/wk and with both doses of ND but not with TE-100 mg/wk (Table 1). In the TE-100 mg/wk group, 4 subjects decreased and 4 increased in weight; body weight increased in each subject

Table 1. Initial (B) body composition and strength measures and change or percent change after 6 weeks of androgen administration (mean \pm SE)

	TE-100 mg/wk (n = 8)		TE-300 mg/wk (n = 7)		ND-100 mg/wk (n = 8)		ND-300 mg/wk (n = 7)	
	B	Change	B	Change	B	Change	B	Change
Body weight (kg)	87.6 \pm 3.3	-0.1 \pm 0.8	88.2 \pm 6.8	3.4 \pm 0.5*	83.2 \pm 1.8	2.7 \pm 0.5*	83.6 \pm 2.5	3.3 \pm 0.6*
Percent body fat from skinfolds	18.3 \pm 1.2	0.4 \pm 0.4	20.8 \pm 2.0	-0.7 \pm 0.5	20.1 \pm 1.0	-0.3 \pm 0.8	17.3 \pm 1.6	1.1 \pm 0.8
Sum of 4 skinfolds (mm)	46 \pm 4	1.7 \pm 1.3	53 \pm 5	-3.0 \pm 1.7	54 \pm 7	-1.9 \pm 4.3	42 \pm 6	3.1 \pm 2.1
<i>Isokinetic tests (Nm)</i>		%Change		%Change		%Change		%Change
60°/s elbow flexion	75 \pm 5	7.1 \pm 9.1	80 \pm 8	17.8 \pm 10.8	78 \pm 5	4.9 \pm 3.8	73 \pm 4	8.4 \pm 5.0
240°/s elbow flexion	57 \pm 5	4.1 \pm 9.7	60 \pm 5	27.3 \pm 11.8**	59 \pm 4	4.1 \pm 7.0	54 \pm 3	6.2 \pm 3.1
60°/s knee extension	245 \pm 16	-0.1 \pm 4.2	256 \pm 10	11.6 \pm 7.2**	239 \pm 19	5.2 \pm 4.3	238 \pm 16	6.1 \pm 4.0
240°/s knee extension	144 \pm 14	8.2 \pm 8.8	150 \pm 8	15.0 \pm 4.2	141 \pm 11	12.2 \pm 4.4	154 \pm 10	7.8 \pm 3.3

* P = < 0.05, paired t test comparison of pre- and post-values.

** P = < 0.05, Dunnett test comparison of % change to TE-100 mg/wk; 1 subject from the low dose group was unavailable for strength measures at the end of the study.

TE, testosterone enanthate; ND, 19-nortestosterone decanoate.

in the other 3 treatment groups, except for 1 subject with a -0.5 kg change in the ND-100 mg/wk group. There were no changes in 4 skinfold thickness measurements (biceps, triceps, subscapular and suprailiac), in the sum of the 4 skinfolds, or in the percent body fat estimated from age and sum of skinfolds (Table 1). Of 15 circumference measurements, only 2 demonstrated any significant change with drug administration: shoulder circumferences increased (3.3 \pm 0.6 cm) with TE-300 mg/wk, and shoulder and chest (at maximum inspiration) circumferences increased (3.8 \pm 1.0, 3.9 \pm 1.6 cm) with ND-300 mg/wk.

Strength increased significantly during the experiment for both knee and elbow measurements in all groups, except the TE-100 mg/wk group, where knee extension at 60°/s did not change. The improvements were greatest in all tests with TE-300 mg/wk treatment but this trend was not significantly different from the improvements in the other treatment groups by ANOVA. When these improvements (as percent change) were compared to those produced by the TE-100 mg/wk group, only the TE-300 mg/wk group showed significantly greater improvements (in 2 out of the 4 measurements) (Table 1). For the measurement demonstrating the largest improve-

ment (elbow flexion, 240°/s), percent change in measured strength was significantly correlated with serum testosterone measured after 6 weeks of treatment among the men receiving either dose of testosterone (r = 0.60; P < 0.03).

Some established markers of androgen action changed in all groups (serum LH and FSH were suppressed) and others changed only in the 2 high dose groups (SHBG and apolipoprotein A-1 levels were reduced) (Table 2). Serum lipids were relatively unchanged except for a small but significant increase in cholesterol/HDL-cholesterol ratio in the ND-300 mg/wk group. Other changes suggested differences between the 2 androgens (reduction in sperm count and mean reduction in testicular volume tended to be less in the ND-100 mg/wk group). Only 2 subjects receiving ND-100 mg/wk demonstrated a reduction in testicular volume, while most individuals in the other groups exhibited a reduction; due to the high variability in this measurement, there were no significant changes in any one group. Testosterone reflected the exogenous androgen treatment, with no significant difference from baseline after 6 weeks of TE-100 mg/wk, while increasing 3-fold with TE-300 mg/wk and decreasing in both ND groups. Estradiol-17 β followed the same pattern of change (Table 2),

Table 2. Markers of exogenous androgen administration before (B) and during (D) androgen administration (mean \pm SE)

	TE-100 mg/wk (n = 8)		TE-300 mg/wk (n = 7)		ND-100 mg/wk (n = 8)		ND-300 mg/wk (n = 7)	
	B	D	B	D	B	D	B	D
LH (IU/l)	5.8 \pm 0.6	2.2 \pm 0.5*	5.7 \pm 0.4	2.5 \pm 0.4*	5.7 \pm 0.4	3.4 \pm 0.5*	7.0 \pm 0.8	2.4 \pm 0.6*
FSH (IU/l)	5.9 \pm 1.2	2.0 \pm 0.3*	6.5 \pm 1.3	1.6 \pm 0.2*	4.3 \pm 0.4	2.0 \pm 0.3*	5.1 \pm 0.8	2.0 \pm 0.3*
Testosterone (nmol/l)	28 \pm 2	34 \pm 2	28 \pm 5	86 \pm 6*	23 \pm 1	10 \pm 2*	34 \pm 4	10 \pm 1*
Estradiol (pmol/l)	116 \pm 16	110 \pm 21	117 \pm 17	290 \pm 34*	112 \pm 11	40 \pm 11*	146 \pm 22	50 \pm 6*
SHBG (nmol/l)	23 \pm 2	20 \pm 2	26 \pm 5	20 \pm 4*	20 \pm 2	21 \pm 3	24 \pm 3	19 \pm 3*
Apolipoprotein A-1 (g/l)	1.49 \pm 0.08	1.37 \pm 0.08	1.53 \pm 0.11	1.28 \pm 0.07*	1.34 \pm 0.06	1.35 \pm 0.07	1.61 \pm 0.14	1.28 \pm 0.11*
Sperm count (million/ml)	50 \pm 3	15 \pm 2*	104 \pm 10	25 \pm 6*	91 \pm 13	35 \pm 5*	76 \pm 7	28 \pm 4*
Testicular volume (cm ³)	30 \pm 3	19 \pm 3	33 \pm 3	19 \pm 1	28 \pm 2	29 \pm 4	35 \pm 3	24 \pm 1

Gonadotropin concentrations represent two samples drawn on separate days for each individual; "D" for the other parameters represents values from the first blood sample drawn 2-3 days after the 6th dose; * P < 0.05, paired t test.

while estrone only increased significantly with TE-300 mg/wk (data not shown). Serum prolactin levels were unchanged, as were indicators of prostate function (semen volume and fructose concentrations).

DISCUSSION

High dose androgen administration produced linear increases in weekly measurements of body weight. This weight change reflected a change occurring primarily in the fat-free component since an increase in fat weight would have been detected by an increase in skinfold thicknesses and abdominal circumferences; this is also consistent with our previous observations using underwater weighing of men treated with high dose TE for 12 weeks [17]. The average weight gain produced by 300 mg/wk of these two parenteral androgens is comparable to the 3.3 kg increase reported for a group of men with similar characteristics following 6 weeks of treatment with 100 mg/day methandrostenolone [18], the orally active androgen which is most frequently used by athletes. These changes appear to involve a specific myotrophic action rather than simply the water retention suggested from some earlier investigations [19]. This is suggested by observed increases in fiber size in muscle biopsies [20] and by increases in total body potassium and nitrogen [21] but the precise nature of these changes remains to be defined. Our circumference results are consistent with studies which demonstrate a preferential effect of androgens on muscle size in the upper body in castrated animals [2], and with clinical observations in humans of androgen-induced increases in upper body muscle mass in female-to-male transsexuals and in androgen replaced Klinefelter's patients.

In the TE-100 mg/wk group, the absence of change in body weight and the maintenance of serum testosterone levels even with substantial suppression of gonadotropins and reduction in testicular volume indicates that this approximates a replacement dose. In some ways, such a drug "control" group offers a more suitable comparison in double blinded studies than placebo controls; the subjects generally observe a reduction in testicular volume and share with the experimental groups any subtle differences which might be attributed to weekly fluctuations in androgen levels between injections and to the absence of a normal diurnal cycle of testosterone secretion. Our subjects were unable to guess whether they were receiving "low" or "high"

dose androgen, although most of them did not have previous experience with exogenous androgens with which to compare. The observation that ND-100 mg/wk produced a weight gain suggests that the "anabolic" properties of this androgen are enhanced relative to TE. In a previous study, Crist *et al.* [22] found no weight gain effect with ND-100 mg/wk compared to testosterone cypionate (which appears to be virtually identical to TE in terms of pharmacokinetics [9]) and to placebo, although this was a crossover study with only 2 week washout periods and 3 week treatment periods.

Nearly all of the strength measurements in this study improved from baseline values. This could be attributed to a learning effect with the testing procedure itself or to an increased training effort by the subjects during the study. Our subjects were physically fit men who generally participate in group sports and running as part of their regular Army training but the groups were balanced with 2-3 subjects per group who also participated in resistance exercise on a regular basis. Thus, the strength measurements in this study probably reflect passive changes rather than improvements resulting from weight training.

We assume that there are qualitative changes which must occur along with the increase in muscle mass to produce substantial increases in strength. This is suggested by the studies of Hervey *et al.* [21] who found weight gains in both trained and untrained men receiving 100 mg/day methandrostenolone but performance increments only with the experienced lifters [22]. We found no difference in the weight gains produced by high doses of nandrolone and testosterone but our data suggests a difference between the strength changes in these groups; only TE-300 mg/wk demonstrated improvements over TE-100 mg/wk, although a larger sample size might have overcome the problem of high variability in the strength changes and may have also revealed statistical differences with nandrolone. The strength improvements produced by high dose TE are consistent with reports of other testosterone induced changes such as increased aggressiveness and increased motoneuron activity [23].

Several studies suggest a difference between testosterone and nandrolone effects on skeletal muscle. Specific increases in muscle protein synthesis have been demonstrated with TE treatment of men with myotonic dystrophy [24] while another study could not demonstrate such

an effect with ND treatment [25]. Testosterone induced changes in tropomyosin isoforms have been demonstrated in the androgen responsive guinea pig temporalis muscle model [26]; on the other hand, in specialized rat models ND has also been shown to increase myofibril protein content [27]. It would be interesting to know if nandrolone binds with equal affinity to muscle cytosolic androgen receptors [28] and if other differences in the metabolism of testosterone and nandrolone [10, 11] modify the effect of nandrolone on skeletal muscle.

We found little difference in the effects of the two steroids on established markers of androgen action. Gonadotropins were significantly suppressed by both steroids at both doses. Although SHBG levels usually reflect the estrogen-androgen balance, SHBG levels were similarly suppressed by the high doses of ND and TE even though estradiol levels were significantly increased only with TE-300 mg/wk and not with ND-300 mg/wk. Sperm count was suppressed by all doses of the two steroids but was less consistently reduced to low levels by ND-100 mg/wk; nevertheless, a longer period of treatment would be expected to further reduce sperm count to <10 million/ml in all four groups [29, 30]. The accessory sex glands also did not appear to be differentially affected, based on the unchanged androgen-dependent semen fructose concentration.

In summary, differences between the two androgens were noted at the lower dose (100 mg/wk), including an anabolic weight gain effect which did not occur with TE and the suggestion of a reduced effect on testicular function by ND. At a high dose (300 mg/wk), these differences were abolished and the actions of TE and ND were substantially the same, including a similar anabolic weight gain effect. Whether or not these two androgens differentially increase strength remains to be established.

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