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ORIGINAL ARTICLE

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The effects of supplementation with 19-nor-4-androstene-3,17-dione and 19-nor-4-androstene-3,17-diol on body composition and athletic performance in previously weight-trained male athletes

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Abstract The purpose of this study was to determine the effects of 8 weeks of norsteroid supplementation on body composition and athletic performance in previously weight-trained males. Subjects were weight and percent body fat matched and randomly assigned to receive either 100 mg of 19-nor-4-androstene-3,17-dione (N-dione) and 56 mg of 19-nor-4-androstene-3,17-diol (N-diol; 156 mg total norsteroid per day), or a placebo (a multivitamin). Each subject participated in resistance training 4 days/week for the duration of the study. Body composition was assessed via dual-energy X-ray absorptiometry. Circumference measures were taken of a relaxed and flexed arm (maximum circumference of the arm), waist (level of umbilicus), and thigh (15 cm proximal to the patella). Strength was determined with a one-repetition maximum bench press, while force and power were determined with a dumbbell bench press (60% body weight) on a Stratec Galileo force platform. Profile of mood states scores were evaluated for vigor and fatigue. There were no significant changes in any of the parameters measured. In conclusion, low-dose supplementation with N-dione and N-diol does not appear to alter body composition, exercise performance, or mood states.

Keywords Steroid · Norsteroid · Androgen · Exercise · Weight-lifting

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Introduction

Athletes have been using androgens to enhance athletic performance and increase skeletal muscle mass since 1954 (Cowart 1987). Since then, the use of androgens and anabolic substances in competitive sports has become illegal. However, androstenedione and androstenediol have been recently introduced to the supplement market as so called ''legal'' over-the-counter androgens in the United States. In addition, two androgens, 19-norandrostenedione and 19-norandrostendiol, are also supposedly available over-the-counter, in spite of the International Olympic Committee's (IOC) medical commission, sports regulation, and state legislation in Europe and elsewhere. It has been speculated that all of these so-called ''legal'' androgens and supposedly over-the-counter supplements work in a manner similar to nortestosterone (NT) and anabolic steroids (Wilson 1988).

Both androstenedione and androstenediol are precursors of testosterone (T; Hedge et al. 1987). Athletes ingest these particular supplements in the belief that their conversion into T will increase anabolic processes and help build up skeletal muscle mass. A study by Earnest et al. (2000) examined the acute effects of oral treatment with 200 mg of 4-androstene-3,17-dione, 4-androstene-3 beta,17 beta-diol, and placebo (PL) on peripheral plasma T concentration. They found that both androstenedione and androstenediol significantly increased the T concentration when compared to a placebo.

However, androstenedione can also convert directly to estrone, especially in women (Gompel et al. 1986), whereas T is also converted to estradiol. In a study by Rasmussen et al. (2000), plasma T concentrations did not significantly increase, and luteinizing hormone was not significantly repressed after the ingestion of 100 mg of androstenedione daily for 5 days. Nonetheless, the concentrations of estradiol did significantly increase from 0.12 (0.02) to 0.17 (0.02) mM after oral adminis-

tration of androstenedione when compared to pretreatment [0.10 (0.01) nmol/l]. Neither estrone nor estradiol have anabolic effects on skeletal muscle.

Since androstenedione and androstenediol have readily been available, few studies have addressed the chronic effects of the supplementation of these steroids on body composition and exercise performance in humans (Antonio and Sanders 1999; King et al. 1999; Van Gammeren et al. 2000; Wallace et al. 1999; Ziegenfuss and Kerrigan 1999). Of these studies, only Ziegenfuss and Kerrigan (1999) showed improvements in body composition and athletic performance.

Norandrostenedione and norandrostenediol are similar to androstenedione and androstenediol, respectively. However, in norandrostenedione and norandrostenediol, the angular 19th carbon of androstenedione and androstenediol is removed, respectively. This modification will supposedly enhance the anabolic properties of norandrostenedione and norandrostenediol without a conversion to T. One might speculate that norandrostenedione and norandrostenediol confer an anabolic effect in skeletal muscle via direct activation of the androgen receptor (AR), since nandrolone and norsteroids are similarly metabolized. Furthermore, it is clear that nandrolone and several of its derivatives bind to the AR (Bergink et al. 1985; Toth and Zakar 1982), and that the superiority of nandrolone to T with regard to myotropic activity is related to the lack of 5-alpha-reductase activity in skeletal muscle (Toth and Zakar 1982). Therefore, the purpose of this study was to determine whether ingesting a supplement that contains low levels of norandrostenedione and norandrostenediol could affect body composition, athletic performance, and mood states in young, resistance-trained males.

Methods

Subjects

Sixteen healthy men with at least 1 year of resistance-training experience (self-reported) were recruited from the university population via posted advertisements. In order to participate in the study, subjects had to meet the following criteria: (1) 19–35 years of age, (2) not currently taking any type of androgens (legal or illegal), and (3) already performing resistance training at least 3 day/week for the last year. Informed consent was obtained from each subject, and the university's Institutional Review Board approved the experimental procedures. In appreciation of completing the study, subjects were compensated with dietary supplements (whey protein powder) worth approximately 100 U.S. dollars.

Experimental procedure

Subjects were matched for body mass and percent body fat. They were then randomly assigned to a so-called legal norsteroid (19-nor-4-androstene-3,17-dione [N-dione] and 19-nor-4-androstene-3,17-diol [N-diol]) or placebo (multivitamin manufactured by Schiff) group. The placebo contained all of the fat- and water-soluble vitamins (the total dose was equal to the recommended dietary allowance in the USA). Each subject was instructed to swallow two capsules of the above-mentioned norsteroids daily for 8 weeks. The consumption of these pills was verified by the investigators through personal interview with the subjects. The concentrations of N-dione and N-diol were examined by an independent laboratory (San Rafael Chemical Services, Salt Lake City, Utah, USA) using high-pressure liquid chromatography. Specifically, for N-dione and N-diol, a weighed portion of the contents of a composite capsule was dissolved/extracted in 1:1:1 – acetonitrile:methanol:water. The extracts were filtered and then analyzed under the following instrument conditions. High-pressure liquid chromatograph (Hewlett Packard Model 1090 II/L); column 1: Luna 15×0.46 cm $\times$ 3 μm C_8; detector: photodiode array, scanning from 190 to 600 nm, quantitation at 210 nm for N-diol, and 245 nm for N-dione. Data from this independent laboratory showed that there was 28 mg and 50 mg of 19-norandrostenedione and 19-norandrostenediol per capsule, respectively. Thus, in the present study, the total dose consumed daily was 156 mg (i.e., 100 mg of N-dione and 56 mg of N-diol).

All subjects were instructed not to change their dietary habits. Twenty-four-hour dietary recalls were obtained from all subjects before and after intervention. Energy, protein, carbohydrate, and fat intake were determined via computer analysis (Nutribase '98, Phoenix, Ariz., USA). All subjects were also instructed to continue their current resistance-training program for the duration of the study. Subjects provided a training log of a typical week of training. Therefore, the only change that was imposed on each subject was the regular ingestion of the norsteroids or placebo. Neither group was provided with any other dietary supplements during the treatment period.

Testing

After approximately three warm-up sets, subjects were instructed to perform a one-repetition maximum (1-RM) on the supine free-weight bench press. Measures of peak force and power were also obtained by having the subjects perform a supine dumbbell bench press with 60% of their pre-test body weight at a maximum velocity on a Stratec Galileo force platform. The force platform is a plate with transducers that are capable of measuring force and power. The force platform is interfaced with a computer that gives readouts of peak force and peak power. The subjects were given three attempts, and the mean of the three attempts was recorded. During both the 1-RM and force/power tests, subjects had their feet planted on the floor, and hips and scapula on the bench at all times; a slight lumbar lordosis was allowed.

Body composition was assessed via whole-body, dual-energy X-ray absorptiometry (DEXA; Lunar DPX-IQ, Madison, Wisc., USA) using the adult, medium-resolution mode (software 4.6b). The subjects lay on the DEXA machine in a supine position with the palms of their hands on the lateral aspect of their thighs. The subject's lower extremities were placed in a comfortable position within the parameters of the DEXA machine. Each scan lasted approximately 25 min. A single pre-test and post-test scan was performed with the subjects in a fasted state, prior to performance testing. The use of DEXA as a method for estimating body composition has been validated previously (Haarbo et al. 1991; Prior et al. 1991).

In addition, the coefficient of variation for fat mass and lean body mass (LBM) has been estimated to be in the range of 1.8–6.4% and 0.6–3.1%, respectively (Chilibeck et al. 1994; Prior et al. 1991; Pritchard et al. 1993). Unpublished data from our laboratory has shown DEXA measures to have a coefficient of variation of 1.49% and 1.00% for fat mass and bone-free LBM, respectively. To ensure quality control, the DEXA unit was calibrated daily using the standard calibration block provided by the manufacturer. In addition, relaxed and flexed-arm circumferences were taken at the maximum girth of the arm. A waist circumference was taken horizontally at the level of the umbilicus, and a relaxed thigh circumference was taken 15 cm proximal to the superior border of the patella.

Finally, subjects completed a profile of mood states (POMS) questionnaire for vigor and fatigue before and after supplementa-

tion (McNair et al. 1992). A score was compiled for vigor and fatigue for each subject in order to determine whether androgen supplementation changed these parameters.

Statistics

Pre- versus post-supplementation changes in body composition, circumference, exercise performance, and POMS were analyzed using a paired *t*-test. An unpaired *t*-test was used to assess the delta scores between groups for all variables. Statistical significance was set at $P < 0.05$; data are shown as means (SD).

Results

According to the results from an independent laboratory (San Rafael Chemical Services, Salt Lake City, Utah, USA), the amount of the norsteroids ingested daily was 156 mg (100 mg of N-dione and 56 mg of N-diol). There were no significant baseline differences between groups for age, height, body mass, or percentage fat (Table 1). In addition, the reported resistance-training program and dietary intakes did not differ between groups (Table 1). There were no significant pre- versus post-supplementation differences for body composition, circumference measurements, exercise performance, or POMS (Table 2). One subject dropped out of the study due to unknown personal reasons.

Discussion

N-dione and N-diol are norsteroids that can be purchased over-the-counter in the United States, although this is illegal in Europe and according to the IOC's medical commission. Their respective structures are derived via the removal of the 19th carbon of androsten-

Table 1 Subject characteristics. Data are presented as the mean (SD)

Characteristic	Multivitamin placebo ($n=8$)	Norsteroid ($n=7$)	Statistical analysis (between groups)
Age (years)	22.38 (1.85)	22.14 (2.67)	0.85
Height (cm)	180.45 (6.54)	180.34 (5.43)	0.97
Body mass (kg)	89.17 (9.07)	89.98 (17.04)	0.91
Body fat (%)	17.45 (7.31)	17.36 (6.72)	0.98
Reported resistance-training regimen			
Days/week	4.63 (0.74)	4.14 (0.52)	0.15
Sets/session	23.75 (6.58)	28.14 (12.83)	0.40
Reps/set	9.50 (1.41)	8.71 (1.19)	0.24
Sets×reps	227.6 (76.6)	250.0 (130.6)	0.69
Reported dietary intake			
kcal (1 kcal = 4184 kJ)	2659 (817)	2477 (707)	0.65
Carbohydrates (C, in g)	335 (139)	315 (164)	0.80
Protein (P, in g)	148 (68)	135 (66)	0.70
Fat (F, in g)	80 (33)	70 (31)	0.95
Ratio of C:P:F (kcal)	51:22:27	52:22:26	

Table 2 Body composition, exercise performance, and profile of mood states. Data are given as the mean (SD). (*LBM* Bone-free lean body mass, *BMC* bone mineral content, *1-RM* one-repetition maximum, *BP* bench press)

Variable	Multivitamin placebo ($n=8$)		Norsteroid ($n=7$)		*P* values for Δ scores
	Pre	Post	Pre	Post	
Body composition					
Body mass (kg)	89.17 (9.07)	90.34 (9.39)	89.98 (17.04)	89.30 (15.15)	0.32
Body fat (%)t	17.45 (7.31)	18.30 (6.35)	17.36 (6.72)	16.43 (7.27)	0.27
LBM (kg)	70.12 (5.80)	70.83 (5.87)	70.27 (10.88)	70.88 (10.04)	0.91
Fat mass (kg)	16.19 (8.19)	17.19 (7.24)	16.33 (7.97)	15.35 (8.13)	0.23
BMC (kg)	4.09 (0.51)	4.17 (0.53)	4.17 (0.74)	4.20 (0.77)	0.35
Circumference measurements (cm)					
Relaxed arm	37.06 (3.33)	37.38 (3.32)	37.00 (5.49)	36.86 (4.36)	0.59
Flexed arm	39.81 (3.59)	40.09 (3.53)	39.79 (5.16)	39.82 (4.72)	0.72
Waist	86.53 (6.12)	85.63 (6.02)	87.68 (9.35)	85.43 (8.39)	0.41
Thigh	56.09 (4.69)	56.31 (4.09)	55.18 (7.46)	55.93 (6.41)	0.54
Exercise performance					
1-RM on BP (kg)	128.69 (19.24)	132.39 (18.69)	124.68 (37.05)	135.71 (34.61)	0.32
Mean peak force (kN)	1.05 (0.24)	1.04 (0.22)	1.02 (0.21)	0.97 (0.24)	0.88
Mean peak power (kW)	0.78 (0.30)	0.77 (0.51)	0.81 (0.64)	0.72 (0.37)	0.99
Profile of mood states					
Vigor	20.9 (3.0)	20.0 (6.1)	21.1 (6.2)	18.7 (5.8)	0.56
Fatigue	11.0 (5.2)	11.0 (5.1)	10.9 (4.0)	11.0 (5.1)	0.96

edione (A-dione) and androstenediol (A-diol). T and 19-NT are illegal androgens in sports (i.e., if they are to be used, the athlete needs a physician's justification and prescription), and also have the same relationship with each other as A-dione and A-diol. When T is 5-alpha-reduced to dihydrotestosterone (DHT), its androgenic properties are amplified due to its higher affinity for the AR (Sundaram et al. 1995; Wilson 1988). Both NT and its 5-alpha-reduced metabolite have reduced androgenic and anabolic properties as compared to T and DHT, due to a reduction in their affinity for the AR (Sundaram et al. 1995; Wilson 1998). Thus, one might surmise that N-dione and N-diol confer an effect similar to NT in that they are metabolized in part to nandrolone and might therefore act either directly or indirectly on the AR. Whether this would result in muscle protein accretion is unknown to the biochemist and physiologist, but not to the athletes themselves.

The present study is the first to examine the effects of small daily doses of N-dione and N-diol supplementation on body composition, strength, and mood states in weight-trained males. Our subjects were similar in age, height, and body mass to the subjects in the study by Ziegenfuss and Kerrigan (1999) who were, however, taking 450 mg of steroid and norsteroid daily. On the other hand, the subjects in the study by King et al. (1999) had a greater percentage of body fat than our own studied population (21.3–23.5% for King et al. versus 17.4–17.5% for the current study).

Subjects did not submit to an endocrinological check up either before or after completion of the study. This may have confounded our results. Nonetheless, in order to participate, subjects were required to have at least 1 year of resistance-training experience (average frequency of 3 sessions/week). We chose not to provide a specific training regimen for these subjects; however, both groups of subjects followed a similar regimen before and during the investigation. Thus, any changes in body composition or strength would therefore be ostensibly due to supplementation with N-dione and N-diol, although it would be difficult to observe improvements in strength as all subjects were already well-trained.

The administration of 100 mg of N-dione and 56 mg of N-diol daily for 8 weeks did not alter LBM or limb circumference measurements when compared to a placebo. The circumference measurement data are consistent with the study by King et al. (1999), where a dose of 300 mg/day of androstenedione produced increases in circumference measurements not significantly different from that of the placebo group. Our LBM data are also consistent with previous studies that have examined A-dione and/or A-diol supplementation. Indeed, a case study of a highly-trained bodybuilder showed no change in body mass, but a slight increase in percent body fat (7.3% to 8.7%, estimated via DEXA) after the administration of 200–400 mg/day of A-dione for two, 4-week cycles, interspersed with 1-week-off (Antonio and Sanders 1999). King et al. (1999) administered 300 mg/day of A-dione for 8 weeks to their subjects. They found a significant increase in LBM (61.2–64.1 kg and 63.1–66.0 kg for the treatment and placebo groups, respectively) and a significant decrease in body fat (19.3–17.1 kg and 18.0–17.2 kg for the treatment and placebo groups, respectively), as estimated by hydrostatic weighing. However, these changes were not significantly different between the groups. One explanation for the apparent increase in LBM for King et al. (1999) may be the fact that untrained subjects were used for the study. It would be reasonable to expect increases in LBM following a resistance-training regimen in untrained individuals. The study by Wallace et al. (1999) showed slight increases in LBM following the twice-daily administration of 50 mg A-dione for 12 weeks, but these increases were not significantly different when compared to the control group. The case studies by Van Gammeren et al. (2000) showed slight increases in LBM (67.9–69.0 kg) and percent body fat (13.9%–14.4%), as measured using DEXA, after ingesting 150 mg/day of a combination of androgens consisting of mostly A-diol for 6–10 weeks. The only study thus far to have shown significant increases in LBM is by Ziegenfuss and Kerrigan (1999). In this 4-week study, the administration of 150 mg, three times per day (total dose of 450 mg/day), of the same combination of androgens used by Van Gammeren et al. (2000) showed increases in LBM (+0.8 kg, 1.1%; as measured using the seven-site skinfold method. Since a higher dosage was administered for the steroid supplement in the previous study (Ziegenfuss and Kerrigan 1999), this might explain the increase in LBM. However, Ziegenfuss and Kerrigan (1999) also used a seven-site skinfold method for body composition determination. Future work should confirm these results via hydrostatic weighing, air displacement plethysmography, or DEXA at the same supplementation dose per day.

An increase in plasma T subsequent to A-dione or A-diol consumption has been proposed as a possible mechanism for muscle protein accretion. Work by Earnest et al. (2000) has demonstrated that oral administration of A-dione and A-diol can significantly increase plasma total and free T. However, chronic administration of 300 mg/day of androstenedione for 8 weeks has also been shown to elevate serum estradiol and estrone in men, as is already known to occur in women (Gompel et al. 1986; King et al. 1999). Thus, one might also speculate that any anabolic effect of A-dione may be offset by the rise in plasma estrogens. For instance, free estradiol was found to significantly increase with obesity in men (Kley et al. 1980). However, it is unknown whether the conversion to estrogens subsequent to A-dione and A-diol supplementation (Broeder et al. 2000) results in eventual gains in fat mass. Certainly, one could speculate that the anabolic properties conferred via the conversion of A-dione to T might offset any possible fat mass accrual as a result of plasma estradiol elevation. Moreover, this transformation to estrogens is not clear for A-diol.

Unlike A-dione, and possibly A-diol, the anabolic and androgenic properties of N-dione and N-diol could

result from their direct binding to the AR (Dorfman 1966). Moreover, nandrolone administration has been found to produce a significant increase in plasma estrone (Bijlsma et al. 1982). This, however, does not mean that such a transformation (to an estrogen) completely impedes the anabolic properties of this particular steroid. Nonetheless, we would speculate that the effect of N-dione and N-diol supplementation may be dose-dependent, and that plasma androgen concentrations did not increase sufficiently in the current study to promote gains in LBM.

The current study also showed no significant increases in strength within or between groups. These results are consistent with several previous studies. Wallace et al. (1999), who administered 100 mg A-dione per day to their subjects, showed slight, but insignificant increases in strength (5.7 kg) via the 1-RM for the bench press and leg press. However, Van Gammeren et al. (2000), who administered 150 mg per day of A-diol to their subjects, primarily showed slight increases in right-leg extensor peak torque (20.6 to 26 kg · m). King et al. (1999), who administered 300 mg per day to their subjects, showed a significant increase in strength from pre- to post-supplementation for both groups, but no significant difference between groups. These differences are probably due to the fact that our study used trained individuals (i.e., at least 1 year of resistance-training experience), while the study by King et al. (1999) used untrained individuals. By using untrained subjects, one would expect to see more obvious gains in strength with the incorporation of resistance training. Rapid increases in strength will usually be seen in the first 4–8 weeks of resistance training, due to neural adaptations (Sale 1988). Moreover, with a higher dosage (450 mg/day of A-diol), and contrary to our study, Ziegenfuss and Kerrigan (1999) showed a significant increase in vertical jump height.

The current study showed no significant differences within or between groups for vigor or fatigue, as determined by the POMS checklist. Conversely, Pope and Katz (1988) have examined the psychological effects of anabolic steroid use. They have shown androgen users to have an array of symptoms such as auditory hallucinations, paranoid delusions, delusions of reference, manic episodes, and depression; but experts have questioned the relevance of this study since there was no control group. Bahrke et al. (1992), who also studied androgen users, showed no significant differences in aggression/hostility or tension/anxiety when compared to a control group. They also found no correlation between androgen dosage and increases in psychological tests. In a review paper, Street et al. (1996) speculated that increases in aggression could be a result of how the individual perceives him/herself vis-à-vis changes in skeletal muscle mass. That is, as one gains muscle mass subsequent to heavy resistance-training combined with androgen use, an individual might appear to be more intimidating to those who are smaller or weaker. This person may then act on the perceived fear of other individuals by behaving more aggressively. Indeed, an important confounding variable in many of these psychological studies is that all subjects might not convey all of the mental problems they might have when using or not using androgenic steroids or related substances.

Finally, our data on the subjects' dietary recalls showed that there were no significant differences between groups for the amount of kilocalories, protein, fat, or carbohydrates consumed. Thus, we can probably eliminate dietary factors in the modification of the treatment or placebo groups. It has been suggested that 3-day diet records be used since they take into account fluctuations in an individual's diet from day to day (Bingham 1991). Also, individuals tend to underestimate the size of portions and/or not report some foods on their diet recall (Krebs-Smith et al. 2000). An increase in the number of days for which dietary observations are noted may improve the accuracy of our data. However, it is possible that the 24-h dietary recalls do not accurately reflect daily eating habits.

In summary, the daily oral supplementation of 100 mg of N-dione and 56 mg of N-diol for 8 weeks had no effect on body composition, muscular strength, muscular power, or mood states in previously weight-trained male athletes. Future research should examine the use of higher dosages and longer treatment durations together with simultaneous and more accurate measurement of endocrinological parameters.

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