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Higher Testosterone Dose Impairs Sperm Suppression Induced by a Combined Androgen-Progestin Regimen

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Abstract

In this study we compared the effects of high-dose and low-dose testosterone enanthate (TE) administered with the same dose of cyproterone acetate (CPA). Eighteen men aged 21-45 were treated with CPA 5 mg/day and with TE 100 mg/week (n = 9; CPA-5-100) or TE 200 mg/week (n = 9; CPA-5-200) for 16 weeks. Semen analyses were performed every 2 weeks; physical examination and chemistry, hematology, gonadotropin, and testosterone measurements were performed every 4 weeks. At week 16 of treatment, sperm counts were significantly more suppressed in the CPA-5-100 group than in the CPA-5-200 group. Sperm counts returned to baseline in all subjects after hormone administration ceased. No difference in gonadotropin levels was found at any time between the 2 groups. During the treatment phase, testosterone levels were significantly higher in the CPA-5-200 group than in the CPA-5-100 group. The present study confirms that CPA/TE administration induces profound sperm suppression. An increase in the dose of androgen resulted in less profound sperm suppression despite no difference in gonadotropin suppression. These data suggest that high testosterone levels can maintain sperm production in men.

Key words: Spermatogenesis, cyproterone acetate, contraception, hormones

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The major challenge in the development of a hormonal male contraceptive is the induction of uniform and consistent sperm suppression in all subjects without producing side effects. A direct relationship between pregnancy rate and sperm concentration has been reported when spermatogenesis

is suppressed to fewer than 5 million/mL, and preliminary data indicate that azoospermia might be the gold standard for achievement of an optimal contraceptive protection (World Health Organization [WHO], 1990, 1996). However, no regimen so far has been reported to induce consistent azoospermia in all subjects. Although there are subjects in whom even a relatively small steroid load is able to induce azoospermia, a percentage of subjects do not achieve azoospermia even after receiving high hormonal dosages (WHO, 1995; Matsumoto, 1988). Significant differences in gonadotropin suppression have not always been found among subjects who achieve azoospermia compared with those who remain oligospermic after hormone administration (Wallace et al, 1993; Behre et al, 1995). The reasons for these interindividual differences in sensitivity to steroids are unknown (Handelsman et al, 1995). Differences in pituitary sensitivity to steroids (Wang et al, 1998), testicular structure (Johnson et al, 1998), genetic background (Dowsing et al, 1999), diet (Suhana et al, 1999), and so on are being tested as possible factors that influence sensitivity to steroids.

Regimens that combine androgens with different progestins such as levonorgestrel, desogestrel, medroxyprogesterone acetate, cyproterone acetate (CPA), or norethisterone enanthate have been shown to be most promising for achieving optimal spermatogenic suppression (Bebb et al, 1996; Handelsmann et al, 1996; Meriggiola et al, 1996, 1997, 1998; Anawalt et al, 1999, 2000; Kamischke et al, 2001; Kinniburgh et al, 2001). In preliminary pilot studies, the prototype regimen, based on combined administration of 100 mg/week of TE with CPA at 100, 50, 25, and 12.5 mg/day has been reported to suppress sperm production below 1 million/mL in all subjects, whereas 85% of subjects (17 of 20) became azoospermic. Suppression of spermatogenesis was dependent on the dose of CPA, and azoospermia was induced in all subjects with 100 and 50 mg/day of CPA, in 75% of subjects (4 of 5) with CPA at 25 mg/day, and in 60% of subjects (3 of 5) with 12.5 mg/day of CPA administered in combination with TE at 100 mg/week. A decrease in hemoglobin and hematocrit that could potentially blunt the acceptability of this contraceptive regimen was also reported. This decrease in hematological parameters was related to the dose of CPA because decreasing the antiandrogen dose also led to a reduction in hemoglobin and hematocrit (Meriggiola et al, 1996, 1998).

In this study we tested whether a further decrease in the dose of CPA to 5 mg/day combined with the same dose of TE (100 mg/week) used in previous studies could completely abolish the decrease in hematological parameters. However, because the combination of CPA at 12.5 mg/day with TE at 100 mg/week has already been shown to not induce azoospermia in all subjects, the dose of 5 mg/day of CPA was expected to result in even more incomplete spermatogenic suppression. Therefore, in another group of men, a higher dosage of TE (200 mg/week) was administered in combination with CPA at 5 mg/day to evaluate whether the increase in androgen dose could balance the decrease in progestin dose, and whether it could improve profound gonadotropin suppression and thus, sperm suppression.

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Population

Eighteen men were recruited through the local mass media. Among men who responded to the announcement, those aged 21-45 years who were healthy by medical history, physical examination, and laboratory tests were enrolled in the study. All enrolled men had basal luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone levels within normal ranges for our laboratory, and sperm counts greater than 20 million/mL after 2-7 days of abstinence (WHO, 1992). All volunteers signed a consent form to participate in the trial. The study was approved by the ethical committee of S. Orsola Hospital and the University of Bologna.

Study Design

Subjects underwent a 3-week control phase in which they provided at least 3 semen specimens, 3 blood draws, and underwent a physical examination. After completing the control phase, subjects were randomly divided into 2 groups; one received CPA 5 mg/day plus TE 100 mg/week (n = 9; group CPA-5-100), whereas the other group received CPA 5 mg/day plus TE 200 mg/week (n = 9; group CPA-5-200) for 16 weeks. During this treatment period, subjects underwent monthly blood draws and biweekly semen analysis. Following the treatment period, subjects entered the recovery phase, which included 3 blood draws, physical examinations every 4 weeks, and biweekly sperm counts until each subject had at least 2 sperm counts that were within his own baseline values.

Measurements

Physical examinations included blood pressure, height and weight, and testis volume measurement (with a Prader orchidometer). Sperm count was performed according to WHO criteria (1992). Azoospermia was defined as no sperm found in a sample after centrifugation and analysis of the pellet.

Measurements were performed in each blood sample for reproductive hormones (LH, FSH, and testosterone), clinical chemistry (total cholesterol, triglycerides, high-density lipoprotein [HDL]-cholesterol and low-density lipoprotein [LDL]-cholesterol, glucose, urea creatinine, total bilirubin, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase), and hematology (hemoglobin, hematocrit, and red blood cells).

Serum levels of LH and FSH were measured by a fluoroimmunoassay (Autodelfia; Wallac, Turku, Finland). The minimum sensitivity was 0.3 IU/L and 0.1 IU/L for FSH and LH assays, respectively. The interassay coefficient of variation (CV) in the high, medium, and low parts of the standard curve were 9.5%, 12.5%, and 11.2% for LH; and 6.2%, 6.1%, and 17.9% for FSH. The intraassay CV in the high, medium, and low parts of the curve for LH and FSH assays were 2.6%, 3.2%, and 7.6%; and 2.7%, 2.9%, and 6.8%, respectively. Serum testosterone levels were measured by radioimmunoassay using reagents from the WHO-matched reagent program by methods previously described (Matsumoto et al, 1983). The assay sensitivity was 0.017 nmol/L; the intraassay and interassay CVs were 5.1% and 9.8%, respectively. Samples from the CPA-5-100 and CPA-5-200 groups were measured in the same assay. Chemistries and hematological measurements were performed by routine assays according to previously described procedures (Meriggiola et al, 1996).

Statistics

Data are reported as mean values ± SEM. The normal distribution of the data was tested by means of the Kolmogorov-Smirnov test (Siegel, 1956) and, when necessary, data were log-transformed before analysis. Azoospermic samples were extrapolated using the linear regression observed between the log sperm counts and their ranks. The frequency of azoospermia and the time for spermatogenesis to return to baseline were compared between the 2 treatment groups by means of the Fisher exact and the Mann-Whitney tests, respectively (Siegel, 1956). Statistical evaluations were performed by running the SPSS/PC+ package on a personal computer (SPSS/PC+, 1992; Chicago, Ill). Two-tailed *P* values less than .05 were considered statistically significant.

Results

Of the initial 18 recruited subjects, 16 completed the study (9 in the CPA-5-100 group and 7 in the CPA-5-200 group). One subject dropped out of the study

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after 8 weeks of hormone administration for personal reasons unrelated to the study and was excluded from the analysis. One subject was found to have thyroid disease and was not included in the analysis.

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Spermatogenesis

No significant differences in sperm counts were detected between the 2 groups at baseline and among the 3 baseline samples (Table 1 and Figure 1).

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Table 1. *Baseline characteristics of the two groups of volunteers*

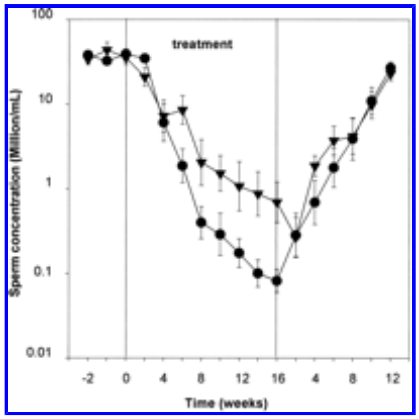

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Figure 1. Mean sperm concentrations in men receiving CPA 5 mg/day plus TE 100 mg/week (•) or CPA 5 mg/day plus TE 200 mg/week (▼) during baseline (weeks -2, -1, and 0), 16 weeks of hormone administration, and 12 weeks after stopping hormone administration.

Both CPA-5-100 and CPA-5-200 regimens induced a profound suppression of spermatogenesis (Figure 1). In the CPA-5-100 group, sperm counts were significantly lower than baseline from week 4 to the end of hormone administration. In the CPA-5-200 group, sperm counts were significantly lower than baseline by week 2 and remained significantly lower until the end of hormone administration. At week 2, mean sperm counts were significantly higher in the CPA-5-100 group than in CPA-5-200 group (P = .020). From week 6 to week 16, sperm counts were significantly lower in the CPA-5-100 group than in the CPA-5-200 group. At week 16, 5 of 9 subjects in the CPA-5-100 group were azoospermic (55.6%). One subject in this group exhibited azoospermia at weeks 10, 12, and 14 and had a sperm count of 0.1 at week 16. The other 3 subjects had sperm counts less than 1 million/mL at week 16. In the CPA-5-200 group, at week 16, 4 subjects had sperm counts less than or equal to 1 million/mL, 2 subjects had sperm counts between 1 and 3 million/mL, and 1 subject had a sperm count of more than 3 million/mL. Significantly more subjects in the CPA-5-100 group achieved azoospermia (55.6%) than those in the CPA-5-200 group (none; P = .034). After stopping hormone administration, sperm counts returned to baseline levels in all subjects. The mean time to return to baseline was 11.1 ± 0.7 and 14.6 ± 1.0 weeks in the CPA-5-100 and CPA-5-200 groups, respectively (P = .017).

Hormones

No significant differences in LH, FSH, and testosterone were detected between the 2 groups at

baseline and among the 3 baseline samples (Table 1 and Figure 2).

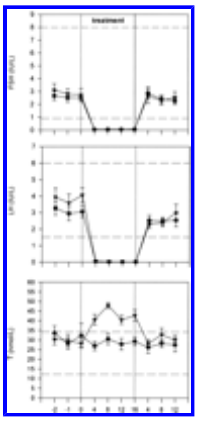

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Figure 2. Mean (± SEM) hormone concentrations in men receiving CPA 5 mg/day plus TE 100 mg/week (•) or CPA 5 mg/day plus TE 200 mg/week (▼) during baseline (weeks -2, -1, and 0), 16 weeks of hormone administration, and 12 weeks after stopping hormone administration.

FSH and LH were significantly suppressed by week 4 of hormone administration in both groups and remained profoundly suppressed until the end of hormone administration (Figure 2). No significant difference in FSH and LH levels could be detected between the CPA-5-100 and CPA-5-200 groups at any time. In group CPA-5-100, serum testosterone levels did not change at any time throughout the study period. In the CPA-5-200 group, serum testosterone levels were significantly higher than baseline levels from week 4 to week 16 of hormone administration. During this period, testosterone levels were significantly higher in the CPA-5-200 group than in the CPA-5-100 group at all time points. In the recovery phase, FSH, LH, and testosterone returned to values that were not significantly different from baseline in both groups at weeks 4, 12, and 4, respectively.

Clinical Characteristics

No significant differences in baseline demographic and clinical characteristics were found between the 2 groups at baseline (Table 1). At week 16 of hormone administration, HDL-cholesterol and total cholesterol in the CPA-5-100 group and HDL-cholesterol and triglycerides in the CPA-5-200 group showed a significant decrease. All these changes returned to pretreatment levels 12 weeks after hormone administration had ceased. No significant changes were found in any other laboratory tests performed. No significant change in hematological parameters was found in any group at any time, although patients in the CPA-5-200 group exhibited a trend toward higher hematocrit (3.8% ± 1.9% increase) that did not achieve significance at week 16 compared to baseline (P = .101). In both groups, a significant decrease in testis size was reported at the end of hormone administration (Table 2). No significant change in body weight was detected in either group at any time (Table 2).

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Table 2. *Laboratory parameters throughout the study in the two groups of men*

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In this study we compared the effects of 5 mg/day of CPA administered in combination with TE at 100 or 200 mg/ week on gonadotropins, spermatogenesis, and metabolic and hematological parameters. Both regimens induced profound sperm suppression without causing adverse effects. These results confirm and extend previous preliminary studies that demonstrated that this prototype of androgen-progestin regimen effectively suppresses sperm production. In this study we found that even a lower dose of CPA than those previously tested, in combination with TE, can induce profound sperm suppression. Even though no significant differences were found in gonadotropin suppression, the regimen in which the highest dose of TE (200 mg/week) was administered with CPA resulted in a lower degree of sperm suppression. These data provide direct evidence that higher androgen levels may prevent complete sperm suppression in humans.

Our previous studies have suggested that the prototype regimen consisting of the combined administration of CPA (100, 50, and 25 mg/day) and TE (100 mg/week) results in profound and uniform sperm suppression (Meriggiola et al, 1996). In those studies, sperm reduction seemed to be dependent on the dose of CPA. We hypothesized that together with the induction of profound gonadotropin suppression, CPA may also act directly at the gonadal level by blocking the stimulatory effect of androgens on spermatogenesis. After hormone administration, intratesticular testosterone (ITT) has been reported to decrease to about 5% of normal (Morse et al, 1973). Whether these low testosterone levels are able to maintain some level of sperm production in some subjects is unclear. Because of the pharmacokinetic characteristics of TE, high supraphysiological serum testosterone levels can be measured soon after injection (Anderson et al, 1996). These high testosterone levels may contribute to maintaining ITT levels and thus sperm production in some subjects. The antiandrogenic effect of CPA within the testis may counteract ITT and thus result in a more profound and uniform sperm suppression.

Studies performed in animals have indicated that testosterone exerts a stimulatory effect on germ cells. In rats and in nonhuman primates, very low androgen concentrations are sufficient to maintain some level of sperm production in the absence of gonadotropins (Cunningham and Huckins, 1979; Sharpe et al, 1988; Weinbauer et al, 1988; Zirkin et al, 1989; Singh et al, 1995; Meachem et al, 1997; Handelsman et al, 1999). Although no direct evidence exists in humans, various observations suggest that testosterone can play a major role in the maintenance of sperm production in the presence of very low gonadotropin levels in men. Two independent studies showed that no difference in serum fluoroimmunoreactive or bioactive gonadotropins can be detected between men who achieved azoospermia and those who achieved oligozoospermia after weekly injections of 100, 200, or 300 mg of TE (Anderson et al, 1996; Amory et al, 2001). These findings may suggest that factors other than gonadotropin suppression may be involved in degree of sperm suppression induced by TE.

In recent studies, testosterone pellets, a zero-order kinetic androgen formulation, administered together with the progestin depot medroxyprogesterone acetate or with desogestrel, induced a more profound sperm suppression than occurred in studies in which each progestin was given together with TE (Wu and Aitken, 1989; Handelsman et al, 1996; Wu et al, 1999; Kinninburgh et al, 2001). The absence of supraphysiological testosterone levels when testosterone pellets were used may explain the more profound sperm suppression achieved with these regimens. After human chorionic gonadotropin and testosterone administration, qualitatively normal spermatogenesis could be maintained in men. In boys with Leydig cell tumors or with an activating mutation of the LH receptor, evidence of gonadal maturation and sperm development was reported (Matsumoto and Bremner, 1989; Shenker et al, 1993; Weinbauer and Nieschlag, 1996; Gromoll et al, 1998).

In the present study, the higher dose of TE given in combination with the same CPA dose led to an impairment of sperm suppression despite there being no difference in serum gonadotropin levels. It is not clear why increasing the hormonal load does not further suppress gonadotropin levels. It is possible that in the CPA-5-100 group, maximal gonadotropin suppression was already achieved, that the number of subjects was not enough to observe a difference, or that the assay we used was not sensitive enough in the low part of the curve to detect small differences. Regardless of the case, compared with men in the CPA-5-100 group, sperm counts in men in the CPA-5-200 group were not as suppressed and none of the subjects achieved azoospermia, whereas sperm counts in one subject were not suppressed to levels lower than 3 million/mL. In the CPA-5-100 group, sperm counts fell below 1 million/mL in all subjects and 5 of 9 subjects (56%) who completed the study achieved azoospermia. In the CPA-5-200 group, TE induced higher supraphysiological serum testosterone levels that resulted in androgen-related effects such as a 3.8% increase in hematocrit and a 9.6% decrease in HDL-cholesterol. We hypothesized that these higher serum testosterone levels may have also resulted in higher ITT concentrations that may have contributed to the maintenance of high sperm production in this group of men. These data represent the first direct evidence that in humans, testosterone can maintain spermatogenesis.

Both the increase of hematological parameters and decrease of HDL-cholesterol induced by the CPA-5-200 regimen seemed to be slightly lower than previously reported with the administration of 200 mg of TE alone. This observation is consistent with the concept that the addition of 5 mg of CPA may counteract some of the androgenic effects of TE (Bagatell et al, 1994; Anderson et al, 1995; Meriggiola et al, 1995). No significant changes in hematological parameters were found in the CPA-5-100 group, confirming previous data suggesting that the effects of CPA on hematological parameters are dose dependent.

In conclusion, results of the present study confirm and extend previous data that suggested that the prototype CPA/TE male contraceptive regimen induces profound sperm suppression. Increasing the dose of the androgen impairs sperm suppression without causing a noted change in gonadotropin suppression. These data may suggest that higher serum testosterone concentrations may result in higher intratesticular concentrations that can maintain qualitative sperm production in men. They also suggest that in future studies of hormonal male contraception, induction of supraphysiological testosterone levels should be avoided to improve sperm suppression and to avoid androgen-related side effects.

Footnotes

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