

A Combined Regimen of Cyproterone Acetate and Testosterone Enanthate as a Potentially Highly Effective Male Contraceptive*

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ABSTRACT

In this study we tested the effectiveness of the combined administration of cyproterone acetate (CPA) and testosterone enanthate (TE) in suppressing spermatogenesis. After a control phase of 3 months, 15 normal men were randomized to receive TE (100 mg/week) plus CPA at a dose of 100 mg/day (CPA-100; n = 5) or 50 mg/day (CPA-50; n = 5) or TE (100 mg/week) alone (n = 5) for 16 weeks. Semen analysis was performed every 2 weeks. Every 4 weeks, fasting blood samples were drawn for the measurement of LH, FSH, testosterone, estradiol, and biochemical and hematological parameters; subjects underwent a physical examination; and they and their partners filled in a sexual and behavioral questionnaire.

Regardless of the dose, each of the 10 subjects receiving CPA plus TE became azoospermic, whereas only 3 of 5 subjects treated with TE alone achieved azoospermia. Times to azoospermia were 6.8 ± 0.5 , 8.4 ± 1.0 , and 14.0 ± 1.2 weeks in groups CPA-100, CPA-50, and TE alone, respectively ($P = \text{NS}$). Throughout treatment, both gonadotropins tended to be higher in the TE alone group than in the other

groups. This difference was mostly due to the higher gonadotropin levels present in the 2 men treated with TE alone that remained oligospermic. No difference in testosterone or estradiol levels was found among the groups. No significant change in lipoprotein levels or liver function tests could be detected. In the CPA-100 and CPA-50 groups, hemoglobin, hematocrit, and red blood cells were lower at the end of the treatment phase, whereas no change was detected in TE alone group. A tendency for a decrease in body weight was detected in subjects treated with CPA, whereas there was no change in subjects receiving TE alone. At the end of the treatment phase, a decrease in testis size was present in all groups. There was no significant change in sexual function, aggressive behavior, mood states, or satisfaction with relationship in any group.

These results suggest that the combined administration of CPA and TE is very effective in suppressing spermatogenesis and may represent a promising regimen for reversible contraception in males. (*J Clin Endocrinol Metab* 81: 3018–3023, 1996)

CYPROTERONE acetate (CPA) is a synthetic steroid (1,2 α -methylene-6-chlor-pregna-4,6-dien-17 α acetoxy-3,20dion) with potent progestational and antiandrogenic actions. The antiandrogenic action of CPA is based on its ability to competitively inhibit binding of testosterone and dihydrotestosterone to the androgen receptor (1–3). Because of these properties, CPA has been used in many pathophysiological conditions in which androgens play an adverse role, such as male hypersexuality, prostatic cancer, female acne, hirsutism, and androgenic alopecia (3, 4). In earlier studies, CPA was used to suppress male fertility, based on the concept that the threshold for androgen action could be higher in the epididymis than in other sexual glands and, therefore, that CPA could be used as a selective posttesticular antifertility drug (5–7). Further studies did not confirm this hypothesis, but showed that CPA can at least

partially suppress sperm production and sperm motility, alter sperm morphology, and compromise the cervical mucus-penetrating ability of spermatozoa (8–10). However, in these trials, the suppression of spermatogenesis was modest, and azoospermia was only occasionally achieved in a few men (8, 11–16). Moreover, major concerns were raised from these studies regarding the androgen deficiency that long term CPA administration would have caused. It was suggested that these side-effects could be avoided by administering CPA in conjunction with an androgen. Studies in monkeys (17, 18) and one preliminary report in men (19) suggested that such hormonal combinations may induce an effective suppression of spermatogenesis and still maintain androgen-dependent physiological functions. This research was not pursued, and studies on hormonal suppression of spermatogenesis performed in the last decade have concentrated on the use of testosterone, administered alone or in combination with GnRH analogs or progestins (20). In these studies azoospermia was never consistently achieved in all tested subjects (20–26), and side-effects that would greatly hinder the acceptability of these regimens were reported (27, 28).

In this study we tested whether the addition of CPA to TE would induce a more profound suppression of spermatogenesis compared to previous studies. We hypothesized that

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the addition of a progestin with antiandrogenic properties to TE treatment might improve previous results by inducing a more profound suppression of gonadotropins and possibly by blocking the direct stimulatory effect of androgens on spermatogenesis.

Subjects and Methods

Subjects

Fifteen normal Caucasian men, aged 22–44 yr (mean \pm SEM, 31 ± 1.7) volunteered for the study. All men were healthy by medical history, physical examination, and screening lab tests. All of the men had basal sperm counts greater than 20×10^6 /mL as well as gonadotropin and testosterone levels within the normal range. The study was approved by the ethical committee of the S. Orsola Hospital in Bologna, and each man signed an informed consent form.

Clinical protocol

The study protocol consisted of a control period, a 16-week treatment period, and a recovery period that lasted until subjects had at least two sperm counts within their own baseline range. During the control phase, subjects provided three seminal fluid samples, separated from each other by at least 7 days. Three fasting blood samples, separated by at least 1 week, were obtained. During the treatment phase, the subjects provided seminal fluids every 2 weeks and fasting (at least 10 h) blood samples every 4 weeks. Blood samples were drawn before the weekly injections of TE were administered between 1300–1600 h. Samples were stored at -20 C until assayed. Every 4 weeks, volunteers attended the clinic to undergo physical examination and weight and blood pressure measurements. Volunteers and their partners were also asked to complete a sexual and behavioral questionnaire each month (27). Four of five subjects in each group had a stable relationship; one subject in each group was single.

After the control period, subjects were randomly assigned to receive 1) CPA (50 mg twice a day, orally) plus testosterone enanthate (TE; 100 mg/week, im; CPA-100); or 2) CPA (25 mg twice a day, orally) plus TE (100 mg/week, im; CPA-50); or 3) TE (100 mg/week, im; TE alone). The type of treatment for each subject was determined by the study coordinator from a list of randomized sequence.

TE (Test-enat, Geymonat, Frosinone, Italy) was administered in a sesame oil suspension of 1 mL, im, weekly. CPA (Androcur, Schering, Milano, Italy) was taken orally.

Measurements

Semen samples were analyzed according to the WHO laboratory manual (29). Sperm concentration was determined using a Makler Chamber. Azoospermia was defined as no sperm found in a sample after centrifugation and analysis of the pellet. Recovery of sperm count was calculated by considering the first of at least two sperm counts within the baseline range of each subject. Estimation of testis size was performed by orchimeter. LH and FSH were measured with an immunochemiluminometric assay (ICMA; Ciba Corning Diagnostics Corp., Medfield, MA). The sensitivity of the LH ICMA assay was 0.1 IU/L. The intra- and interassay coefficients of variation (CVs) at low, medium, and high levels of the standard curve were 4.3%, 3.2%, and 4.5% (intraassay) and 6.0%, 5.9%, and 5.9% (interassay), respectively. The sensitivity of the FSH ICMA assay was 0.3 IU/L. The intra- and interassay CVs at low, medium, and high levels of the standard curve were 2.7%, 2.2%, and 2.0% (intraassay) and 6.2%, 5.6%, and 7.4% (interassay), respectively. Testosterone was measured in unextracted serum by RIA (Diagnostic System Laboratories, Webster, TX). The sensitivity of the testosterone RIA was 0.3 nmol/L. The intra- and interassay CVs at low, medium, and high levels of the standard curve were 7.0%, 4.3%, and 4.0% (intraassay) and 14.7%, 13.1%, and 16.4% (interassay), respectively. Estradiol levels were measured in unextracted serum by RIA (Diagnostic Products Corp., Los Angeles, CA). The sensitivity of the RIA was 18 pmol/L. The intra- and interassay CVs at low, medium, and high levels of the standard curve were 9.6%, 8.1%, and 7.8% (intraassay) and 17.5%, 11.3%, and 8.3% (interassay), respectively. Hematology (hemoglobin, hematocrit, and red blood cell count), chemistry (total cholesterol, high density

lipoprotein, triglycerides, urea, creatinine, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, phosphate alkaline, and bilirubin), and electrolytes (sodium, potassium, calcium, and phosphorus) were also measured according to previously validated methodologies (30).

Statistics

Multifactorial ANOVA with repeated measures was used to determine differences within each treatment group across time and between study groups for any parameter where appropriate data were log transformed before analysis.

Results

Semen parameters

Baseline sperm concentrations in the three groups were 61.1 ± 12.7 million/mL in group CPA-100, 47.5 ± 3.7 million/mL in group CPA-50, and 49.0 ± 4.7 million/mL in group TE alone ($P = \text{NS}$ among different groups). All men receiving CPA together with TE (CPA-100 and CPA-50) became azoospermic, whereas only three of the five men treated with TE alone achieved azoospermia (Fig. 1). Azoospermia was induced in all men receiving CPA plus TE regardless of the dose of CPA. The mean times to achieve azoospermia were 6.8 ± 0.5 , 8.4 ± 1.0 , and 14.0 ± 1.2 weeks in the CPA-100, CPA-50, and TE alone groups, respectively ($P = \text{NS}$). In group CPA-100, three subjects achieved azoospermia by week 6 and two subjects by week 8. In group CPA-50, azoospermia was achieved by week 6 in one subject,

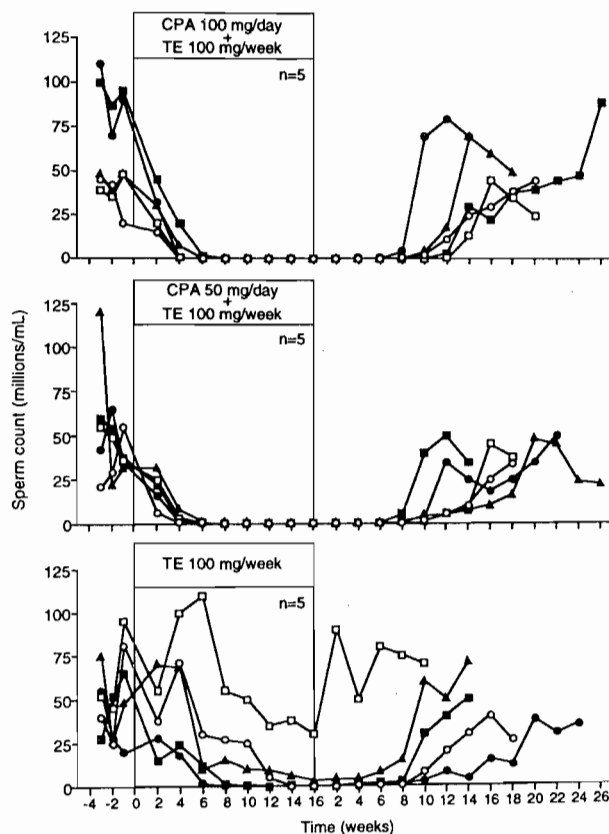


FIG. 1. Sperm concentrations in individual subjects during the control period, throughout 16 weeks of hormone administration and during 26 weeks of the recovery phase.

by week 8 in three subjects, and by week 12 in one subject. In group TE alone, azoospermia was achieved by weeks 12, 14, and 16 in the three subjects, respectively. Once azoospermia was achieved, this condition was maintained until the end of hormone administration in all subjects. Sperm counts of the two men (TE alone group) who did not become azoospermic were 30 and 3 million/mL during week 16. After the end of treatment, sperm counts returned to baseline levels in all men. Mean time to return to baseline was 16.0 ± 2.7 weeks in the CPA-100 group (10–26 weeks), 18.5 ± 1.0 in the CPA-50 group (16–20 weeks), and 14.7 ± 2.9 (10–20 weeks) in the TE alone group ($P = \text{NS}$).

Hormone levels

Mean baseline LH levels were 4.3 ± 0.6 , 5.2 ± 0.9 , and 3.3 ± 0.2 IU/L in the CPA-100, CPA-50, and TE alone groups, respectively ($P = \text{NS}$ among different groups). Mean baseline FSH levels were 2.7 ± 0.3 , 4.5 ± 0.9 , and 2.2 ± 0.45 IU/L in the CPA-100, CPA-50, and TE alone groups, respectively ($P = \text{NS}$ among different groups). Both LH and FSH serum levels were markedly suppressed in all groups (Fig. 2). In all subjects in the CPA groups, gonadotropin levels fell below the sensitivity of the assay by week 4 of treatment and remained undetectable until the end of hormone administration (Fig. 2). In the three men who achieved azoospermia after TE alone administration, gonadotropin levels also fell below the sensitivity of the assay by weeks 8–12 (LH by weeks 8, 12, and 8, respectively; FSH by weeks 8, 4, and 8, respectively). In the two subjects who did not achieve azoospermia after TE alone administration, gonadotropin levels remained slightly higher than those in subjects who became azoospermic. By week 8 of recovery, both LH and FSH had returned to the baseline range in each of the subjects in all groups (Fig. 2). Mean baseline testosterone levels were 11.7 ± 0.15 , 16.3 ± 1.6 , and 14.3 ± 1.0 nmol/L in the CPA-100, CPA-50, and TE alone groups, respectively ($P = \text{NS}$ among different groups). No change in testosterone or estradiol levels could be detected in any group during hormone administration (Fig. 2).

Lipids, blood chemistry, electrolytes, and hematology

No change in lipoprotein levels or liver function tests could be detected in any group. Serum urea levels did not change. Creatinine levels were significantly reduced in the CPA-100 group, whereas no change could be detected in the other groups. No change in serum sodium, potassium, or calcium levels could be detected in any group throughout the treatment period compared to baseline values (Table 1). Serum phosphorus levels did increase in the TE alone group, whereas there was no change in the CPA groups (Table 1). Hemoglobin, hematocrit, and red blood cell levels were lower at the end of the treatment phase in the CPA-treated subjects, whereas no significant changes could be detected in the TE alone group (Table 1). The changes noted returned to basal levels during the recovery phase.

Sexual behavior

There was no significant difference in frequency of sexual intercourse, desires, fantasies, masturbation, kissing, or

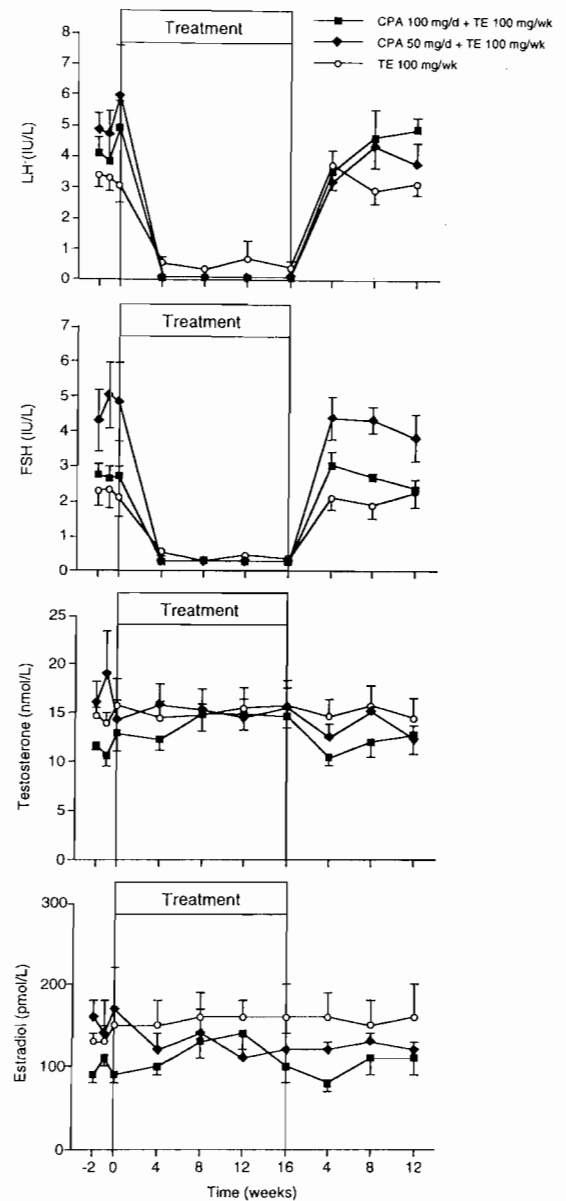


FIG. 2. Mean (\pm SEM) LH, FSH, testosterone, and estradiol concentrations in men treated with 100 mg/week TE plus 100 mg/day CPA, 100 mg/week TE plus 50 mg/day CPA, and 100 mg/week TE alone.

morning erections between control and treatment periods in any group. Measures of aggressive behavior and mood states as reported by both the subjects and their partners did not show any change. There was no change in subjects' satisfaction with their relationships during the treatment period.

Clinical

A decrease in testicular size occurred during the experimental period in all men in each group. At the end of treatment, mean testis volume declined by $54 \pm 2\%$, $43 \pm 4\%$, and $36 \pm 5\%$ in the CPA-100, CPA-50, and TE alone groups, respectively (baseline: 21 ± 1 , 18 ± 3 , and 23 ± 1 mL; week 16: 10 ± 0 , 10 ± 0 , and 15 ± 1 mL in groups CPA-100, CPA-50, and TE alone, respectively). After cessation of hormone ad-

TABLE 1. Levels of lipoproteins and biochemical parameters in volunteers at baseline (mean of three samples), after 16 weeks of hormone administration (week 16), and 12 weeks after stopping hormone administration (recovery)

	CPA (100 mg/day) + TE (100 mg/week)			CPA (50 mg/day) + TE (100 mg/week)			TE (100 mg/week)		
	Baseline	Week 16	Recovery	Baseline	Week 16	Recovery	Baseline	Week 16	Recovery
Total cholesterol (mmol/L)	4.74 ± 0.24	3.83 ± 0.38	4.84 ± 0.54	4.89 ± 0.22	4.28 ± 0.55	4.56 ± 0.28	5.75 ± 0.36	4.85 ± 0.52	5.46 ± 0.47
HDL-cholesterol (mmol/L)	1.09 ± 0.08	1.00 ± 0.09	1.30 ± 0.10	1.22 ± 0.08	1.29 ± 0.08	1.27 ± 0.1	1.16 ± 0.05	1.14 ± 0.13	1.34 ± 0.08
Trygliceride (mmol/L)	2.70 ± 0.03	2.07 ± 0.50	2.58 ± 0.67	2.90 ± 0.45	1.83 ± 0.20	2.36 ± 0.37	3.12 ± 0.41	2.20 ± 0.20	3.25 ± 0.81
LDL cholesterol (mmol/L)	3.04 ± 0.20	2.37 ± 0.33	2.65 ± 0.47	3.09 ± 0.17	2.63 ± 0.57	2.83 ± 0.36	4.06 ± 0.26	3.27 ± 0.60	3.80 ± 0.42
GOT (U/L)	24 ± 2	18 ± 4	19 ± 4	22 ± 2	21 ± 4	17 ± 2	21 ± 1	19 ± 1	21 ± 1
GPT (U/L)	22 ± 3	19 ± 7	21 ± 8	18 ± 1	15 ± 1	15 ± 1	33 ± 4	21 ± 2	26 ± 4
GGT (U/L)	19 ± 3	19 ± 5	22 ± 9	20 ± 2	21 ± 3	23 ± 6	20 ± 2	20 ± 4	26 ± 5
Total bilirubin (μmol/L)	17.1 ± 2.4	17.4 ± 4.8	13.7 ± 4.1	19.2 ± 5.0	21.9 ± 4.6	23.3 ± 10.4	20.7 ± 2.1	24.8 ± 7.0	20.2 ± 4.3
Alkaline phosphatase (U/L)	165 ± 17	127 ± 33	139 ± 34	187 ± 14	147 ± 24	171 ± 28	186 ± 10	159 ± 20	191 ± 19
Urea (mmol/L)	5.3 ± 0.3	4.7 ± 0.3	5.2 ± 0.7	5.3 ± 0.5	5.3 ± 0.7	5.5 ± 0.7	5.8 ± 0.3	6.0 ± 0.2	5.7 ± 0.3
Creatinine (μmol/L)	94 ± 3	86 ± 4 ^a	121 ± 12	92 ± 3	111 ± 8	93 ± 4	98 ± 2	115 ± 9	106 ± 3
Na (mmol/L)	143 ± 1	142 ± 1	142 ± 1	140 ± 1	140 ± 1	143 ± 1	140 ± 1	141 ± 1	142 ± 1
K (mmol/L)	4.2 ± 0.1	3.9 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.2 ± 0.1	3.7 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	3.8 ± 0.3
Ca (mmol/L)	2.6 ± 0.06	2.3 ± 0.03	2.5 ± 0.08	2.3 ± 0.12	2.4 ± 0.07	2.4 ± 0.02	2.4 ± 0.04	2.4 ± 0.08	2.4 ± 0.04
P (mmol/L)	1.30 ± 0.05	1.12 ± 0.07	1.26 ± 0.15	1.03 ± 0.04	1.36 ± 0.15	1.08 ± 0.08	0.91 ± 0.02	1.49 ± 0.12 ^a	0.84 ± 0.06
Hemoglobin (g/L)	154 ± 3	139 ± 5 ^a	150 ± 7	156 ± 3	142 ± 4 ^a	146 ± 7	154 ± 3	158 ± 5	155 ± 5
Hematocrit (%)	44 ± 1	40 ± 1 ^a	43 ± 2	44 ± 7	41 ± 1	46 ± 1	45 ± 1	47 ± 7	46 ± 1
Red blood cells (10 ⁶ /L)	5.1 ± 0.1	4.5 ± 0.1	4.9 ± 0.2	5.4 ± 0.1	4.9 ± 0.1	5.0 ± 0.2	5.2 ± 0.1	5.1 ± 0.2	5.2 ± 0.1

Values are the ± SEM.

^a $P < 0.05$ vs. baseline.

ministration, testicular volumes returned to baseline in each of the subjects. No man was concerned about this enough to stop his participation in the study. Examination of the subjects revealed no enlargement of the liver, no change in blood pressure, and no occurrence of gynecomastia. There was a slight decrease ($P = NS$) in body weight in subjects who received CPA in combination with TE, which was not dependent on the dose of CPA (CPA-100: baseline, 77.9 ± 5.0 kg; week 16, 75.6 ± 3.4 kg; CPA-50: baseline, 81.9 ± 8.4; week 16, 77.9 ± 6.5 kg). No change in weight could be detected in subjects that received TE alone (baseline, 74.1 ± 3.8; week 16, 74.6 ± 4.0 kg). Body weight returned to pretreatment levels in all subjects before the end of the recovery phase. One subject complained of very mild acne during week 14 of TE alone; no other subject in any group reported this problem.

Discussion

In this study we tested the effectiveness of combined administration of CPA and TE in inducing a profound and consistent suppression of spermatogenesis. This hormonal combination was compared to a regimen of TE alone. Regardless of the dose, each of the men receiving CPA became azoospermic ($n = 10$), whereas only three of five of the men treated with TE alone achieved azoospermia. The time to achieve azoospermia was shorter in the CPA groups than in the TE alone group, whereas no significant difference in the time of recovery of spermatogenesis could be detected among the different groups.

Studies of hormonal male contraception have shown that the complete suppression of spermatogenesis leads to an

extremely low fertility rate (21). However, in trials performed to date, azoospermia could be achieved in only 60–88% of Caucasian subjects with the use of TE administered alone or in combination with progestins or GnRH antagonists (20–26, 31, 32). A more profound suppression of gonadotropins and/or a more complete depletion of intratesticular testosterone could improve previously obtained results and lead to a higher rate of azoospermia. Recently, it has been shown that the addition of a high dose of progestin to TE caused a further decrease in gonadotropin levels accompanied by a more consistent suppression of spermatogenesis (26, 33). In the same study (33) and in another trial in which testosterone buciclate was used (34), subjects who became azoospermic or severely oligospermic had lower gonadotropin levels than oligospermic subjects. These data suggest that an insufficient suppression of gonadotropins could explain the inconsistent suppression of spermatogenesis previously reported. However, in animal studies, only the depletion of testosterone from the testis obtained by delaying testosterone replacement led to a quicker and more profound suppression of spermatogenesis (35). In a more recent study in monkeys treated with the same dose of GnRH antagonists, higher doses of testosterone prevented the induction of azoospermia (36). These studies suggest that together with a profound suppression of gonadotropins, a complete blockade of the intratesticular androgen effect may be a key factor for the achievement of a complete suppression of spermatogenesis. Because of its progestational properties, CPA can act at the hypothalamic-pituitary level synergistically with testosterone in suppressing gonadotropins. As an antiandrogen, CPA

could also act at the gonadal level by competitively inhibiting the stimulatory effect of androgens, both of gonadal origin and from other endogenous or exogenous sources. In our study the addition of CPA to TE caused a very quick suppression of both gonadotropins, which became undetectable by week 4 of hormone administration in all 10 subjects. In the TE alone group, gonadotropin levels fell below the sensitivity of the assay only in the subjects who became azoospermic and stayed slightly higher in the two subjects who remained oligospermic. The time until gonadotropins became undetectable tended to be longer in azoospermic subjects receiving TE alone than in subjects treated with CPA plus TE. These data suggest that there is a direct relationship between gonadotropin suppression and the occurrence of azoospermia, and that a more profound suppression of gonadotropins could induce a more complete suppression of spermatogenesis.

The suppression of spermatogenesis that we observed in our study with CPA plus TE is similar to that reported in a preliminary study conducted in India in which lower doses of CPA (20 mg/day) and TE (250 mg biweekly) were used (19). In that study azoospermia was achieved in five of six subjects, and one subject had sperm count of 0.01 million/mL. These data suggest that lower doses of CPA than those used in our study could still produce a profound suppression of spermatogenesis.

We found the decrease in testis size to be greater in CPA-treated subjects than in subjects who received TE alone and also greater than that reported in previous studies (21). Whether this greater reduction of testis volume could be due to the profound gonadotropin suppression that we found in our study or to a direct antiandrogenic effect of CPA on the testis is unclear.

No serious side-effects requiring withdrawal from the study were registered with any hormonal regimen in our study. Of interest is the finding that unlike other hormonal regimens (27, 28, 37), CPA plus TE did not cause any change in high density lipoprotein levels. One subject complained of mild acne during week 14 of TE alone injection, but none of the subjects receiving CPA plus TE at either dose showed any sign of acne. In both CPA groups, a small, but not significant, decrease in body weight was registered. This decrease was not apparently related to the dose of CPA. The addition of CPA to TE also caused a dose-dependent decrease in hematocrit, hemoglobin, and red blood cells. These effects were not present with TE alone. This decrease was probably the result of the antiandrogenic action of CPA and is consistent with the well known action of androgens on erythropoiesis. As the threshold of androgen action differs in various tissues, CPA caused effects that varied among different tissues. Although in our study these side-effects were well tolerated by the subjects, in the long run they could hinder the wide acceptability of this contraceptive regimen, especially if they were to be used in developing countries with marginal nutritional conditions. In a combined regimen using CPA, the doses of testosterone and the antiandrogen could be adjusted to fully maintain important physiological functions such as hematopoiesis while creating testosterone levels that do not stimulate spermatogenesis and do not cause unwanted metabolic side-effects.

In conclusion, this study provides preliminary data showing that the combined administration of CPA plus TE very effectively suppresses spermatogenesis through a profound suppression of gonadotropins. Whether an antiandrogenic action exerted by CPA at the testicular level might have contributed to the high efficacy of this regimen cannot be demonstrated in this study. This regimen was also fully reversible. Additional studies aimed at finding the lowest doses of CPA and testosterone that completely suppress spermatogenesis and fully prevent androgen deficiency hold great promise in the development of a widely acceptable hormonal contraceptive for men.

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