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STUDIES WITH CYPROTERONE ACETATE FOR MALE CONTRACEPTION

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SUMMARY

Daily administration of 10 and 5 mg of cyproterone acetate (CA) to two groups of normal volunteers over a period of 28 weeks caused a gradual decrease in the count and motility of the spermatozoa, with a concomitant increase in the percentage of non-motile as well as abnormal and immature sperms. The ability of motile spermatozoa in the ejaculate to penetrate through preovulatory cervical mucus was markedly inhibited. The levels of acid phosphatase, sialic acid and glycerylphosphorylcholine in the semen decreased progressively, whereas the levels of fructose did not show any significant change. The levels of plasma testosterone were decreased in both the groups. However, the libido and potency were not significantly altered. The liver and kidney functions were not affected. Following cessation of drug therapy the changes in various parameters gradually reversed towards normal values, although some of the parameters did not reach the control level by the 12–18th weeks. In another group of three normal volunteers, who had received 10 mg of CA daily for 12 -16 weeks resulting in a marked decrease in the count, motility and cervical mucus penetrating ability of the spermatozoa, and in the biochemical constituents of the semen, subsequent concurrent administration of 75 mg of mesterolone daily for 6–13 weeks counteracted the CA-induced changes very significantly. The possible sites and mode of action of CA and its potential as a male contraceptive are discussed.

INTRODUCTION

High doses of cyproterone acetate (1,2α-methylene-6-chloropregn-4, 6-diene-17α-ol-3, 20-dione-17α-acetate), which has very strong anti-androgenic and progestational properties, were reported to cause regression of spermatogenesis [1, 2] and reduction of fertility in male rats [2], and inhibition of spermatogenesis, libido and potency in men [3,-5]. Prasad and coworkers[6, 7] reported that micro doses of cyproterone acetate released from subcutaneously implanted silastic capsule caused reversible functional sterility in rats by selective inhibition of epididymal function resulting in loss of fertilizing ability of the spermatozoa. The present investigation [8, 9] was undertaken to find out whether low doses of cyproterone acetate would produce similar differential effect on epididymal activity in the human without affecting the function of the testis and/or other accessory sex organs, and whether the changes produced by cyproterone acetate could be counteracted by concurrent administration of an androgen.

MATERIALS AND METHODS

Study I

Fourteen healthy male volunteers aged between 20–40 years were divided into two equal groups. Following a control period of 8 weeks and a placebo regimen of 10 weeks, the volunteers in groups A and B received orally 10 and 5 mg of cyproterone acetate per day respectively for a period of 28 weeks. They were followed up for 12–18 weeks after cessation of treatment. Semen samples were obtained every fortnight with 3 days abstinence before each sample and blood was collected every 4 weeks throughout the study period.

In semen, the count, motility and morphology of spermatozoa were studied and the levels of fructose, sialic acid, glycerylphosphorylcholine (GPC) and acid phosphatase were determined. The ability of the spermatozoa to penetrate through preovulatory cervical mucus was also tested in some cases. Blood levels of testosterone were determined, and liver and kidney function tests were carried out. Methodology followed were as described earlier [8]. Coital frequency and status of libido were recorded every fortnight.

Study II

Three normal fertile human male volunteers aged between 32–35 years were enrolled for this study. Following a control period, when 3–6 semen samples were collected at 2 weeks' intervals and 2 blood samples were collected at 4 weeks' intervals, daily treatment with 10 mg of cyproterone acetate was initiated. When a very marked decrease in sperm count and motility was noted during cyproterone acetate therapy, 75 mg of mesterolone, a weak androgen with little gonadotropin-suppressing action, was administered daily per oral route concurrently with cyproterone acetate over periods of 13, 12 and 6 weeks respectively. The physical, morphological and biochemical studies carried out with the semen were the same as in Study I. Cervical mucus penetrating capacity of the spermatozoa was also tested. In blood, the levels of SGOT, SGPT, alkaline phosphatase and urea were estimated following the methods reported earlier [8].

RESULTS

Study I

Count, motility and morphology of spermatozoa

Group A. During control and placebo periods (18 weeks), the mean sperm count varied from 87.2 to 126 million per ml with an overall mean of 113.8 million per ml of semen. During therapy period (28 weeks), there was a significant decrease in the mean sperm count at 4 weeks of treatment, which was maintained with minor fluctuation up to the 26th week of therapy; the mean counts ranged from 46 to 83 million/ml. The mean sperm count was elevated during the post-therapy period; however, the count did not return to mean control level upto the 12th week of post-therapy period. In 4 volunteers who were followed upto 16–18th week, although the sperm count showed a further rise it did not reach the respective peak values observed during the control period.

During the control period the mean percentage of good forward moving spermatozoa (range 40–56%) and that of nonmotile spermatozoa (range 12.8–30%) showed minor fluctuations. During the treatment period there was a progressive decrease in the mean percentage of good forward moving spermatozoa, which became zero by the 22nd week of therapy. There was a concurrent increase in the mean percentage of nonmotile spermatozoa from 37.1 to 71.4%. The proportion of sluggishly motile spermatozoa did not show much change during the treatment period. Following withdrawal of the drug the mean percentage of nonmotile spermatozoa gradually decreased to 28.3%, concomitantly with a gradual increase in the percentage of good forward moving spermatozoa. However, at the end of 12 weeks of post-therapy period the respective values of the mean control levels were not reached.

The mean percentage of abnormal forms, which included pin head, giant head or double head, swollen neck and double tailed spermatozoa, and sloughed out spermatids, progressively increased from the second week of drug therapy, and reached up to 35–40% by the end of 22nd week of treatment. Following cessation of therapy the abnormal forms started decreasing. However, by the 12th week of post-therapy period it did not reach the normal control level. In cases who were followed upto the 16–18th week during post-therapy period, the percentage of abnormal forms returned to pretreatment levels.

Group B. The mean values of fortnightly sperm counts during the control period ranged from 70.8 to 110 million per ml with an overall mean of 94.7 million/ml of semen. During therapy the mean sperm count decreased significantly, but the counts showed wide fluctuations (22.8–80.2 million/ml) in this group. Maximum decrease of mean sperm count was observed during 10th week of treatment. Following withdrawal of the drug, the sperm count gradually increased (48–98 million/ml) and reached almost the control level by the 12th week of post-therapy period. The mean percentage of good forward moving spermatozoa (range from 43–62%) as well as that of non-motile spermatozoa (range from 14–25%) showed very little fluctuation. During drug therapy there was a progressive decrease (45–1.4%) in the mean percentage of forward moving spermatozoa with a concomitant increase in the mean percentage of non-motile spermatozoa (37–64.4%). The proportion of non-motile spermatozoa reached the maximum by 20th week of drug therapy, whereas the percentage of good motile sperm decreased to the lowest level by the 24th week of treatment. Following cessation of treatment there was a gradual decrease (50–38.5%) in the mean percentage of non-motile sperm, with progressive increase (10.7–35%) in the mean percentage of good motile spermatozoa. However, even at the 12th week of post-therapy period these values did not reach the mean normal levels. During drug therapy, there was a progressive increase in the percentage of abnormal forms; the highest value of 30% was reached by the 22nd week of therapy. Following withdrawal of the drug the percentage of abnormal form started declining, but normal control levels were not reached by 12th week of post-therapy.

Biochemical constituents of semen

Group A. The mean level of seminal acid phosphatase decreased markedly by the end of 2 weeks of drug therapy and the decrease in the mean level of sialic acid was less rapid but progressive. The level of GPC declined sharply by two weeks of drug therapy and similar low levels with minor fluctuation were maintained during the rest of the treatment period. Seminal fructose levels did not show any significant change at any time of drug therapy. Following cessation of treatment the levels of acid phosphatase, GPC and sialic acid started rising. But only the level of GPC returned to the mean control value by the end of the 12th week of post-therapy period.

No significant change was noted in semen volume during drug therapy and the post-therapy period.

Group B. Acid phosphatase activity in the semen decreased sharply by the end of 4 weeks of drug therapy and progressively decreased thereafter. The level of sialic acid declined slowly but progressively from 6 weeks of drug therapy. The decrease in the mean level of GPC was less marked compared with the acid phosphatase, but it was significant. The mean levels of fructose showed wide fluctuations and the changes during drug therapy were not significant. Following cessation of treatment the levels of all biochemical constituents started rising and by the 12th week of post-therapy period, these reached almost normal levels.

There was no significant change in the volume of the semen.

Penetration of cervical mucus by spermatozoa

Group A. In 4 volunteers of this group the penetrating ability of the spermatozoa through the cervical mucus was assessed by modified Kremer's test. These tests were performed at fortnightly intervals during the 16–26th week of drug therapy and during post-therapy period. In all these cases the ability of the spermatozoa to penetrate through the cervical mucus was decreased: these sperms could enter only 10–20 μmm into the mucus in 30 seconds, whereas the spermatozoa from normal untreated individuals could enter more than 100–200 μmm into the same mucus during the same period. The penetrating ability of the spermatozoa through the cervical mucus was gradually recovered, and by 12th week of post-therapy period the sperm could penetrate 90–120 μmm, through the mucus.

Group B. In 4 volunteers where this test was done during the 16–28th week of drug therapy, the penetration rate of sperm was markedly inhibited. Penetration rates were only 10–20 μmm in 30 seconds, in contrast to 100–120 μmm observed with control semen. During post-therapy period the ability of spermatozoa to penetrate through the cervical mucus returned to normal range of 100–120 μmm by the 12th week.

Status of libido

Group A. There was no change in state of libido in general. Only two volunteers reported decreased libido in the second week of therapy, which lasted only for 15–20 days. In two cases lowered coital frequency was recorded for sometime. However, the volunteers attributed this to the lack of privacy, sickness in the family and/or due to hot summer weather. One volunteer complained of hyper-sexuality during 12–14th week of post-therapy period, which gradually subsided.

Group B. No alteration in the status of libido was observed in this group. One volunteer complained of decreased libido during the placebo period.

Blood level of testosterone

The mean level of plasma testosterone in both groups decreased progressively during drug therapy. During post-therapy period, plasma testosterone level gradually increased and reached almost to the normal control level by 12th week.

Liver and kidney function tests

In both the groups there was no significant change in the levels of SGOT, SGPT, serum alkaline phosphatase and cholesterol, and all were well within normal limits.

An overall analysis of response in individual volunteers

A critical analysis of the response of various parameters in individual volunteers revealed the following:

Group A. The lowest sperm count encountered during drug therapy in different individuals varied from 1.7 to 41 million/ml and the earliest time when the

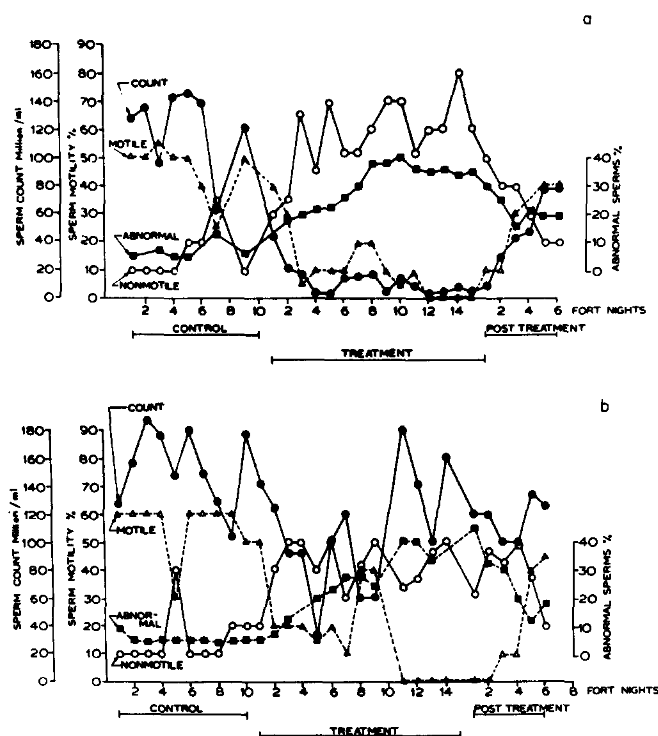

Fig. 1. Note the changes in the count, motility and morphology of the spermatozoa in two volunteers receiving daily 10 mg cyproterone acetate. Volunteer at 1a shows very good response, whereas that at 1b shows moderate response.

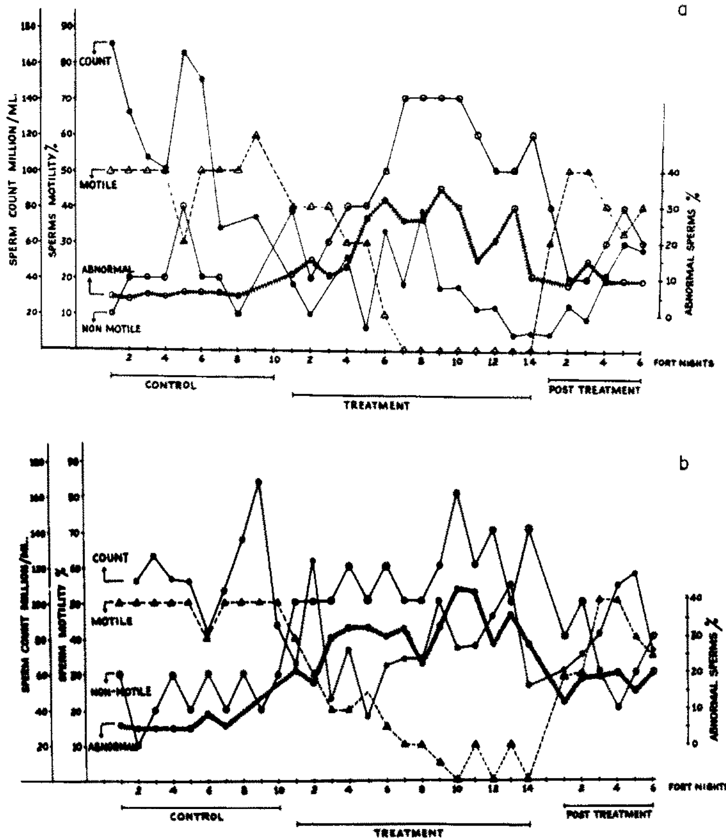

Fig. 2. Note the changes in the count, motility and morphology of the spermatozoa in two volunteers receiving daily 5 mg cyproterone acetate. Volunteer at 2a shows good response, but that at 2b shows a poor response.

lowest count was recorded varied from 6 to 14 weeks of therapy. Those who had initial low counts in control period responded more rapidly and decreased counts varied from one to few million/ml. The percentage of good motile spermatozoa decreased to zero in between 12 to 24 weeks. Similarly the proportion of non-motile spermatozoa reached as high as 72–80% by the 10th to 22nd week. The variations in response of various parameters in individual volunteers are well illustrated in Fig. 1a & b.

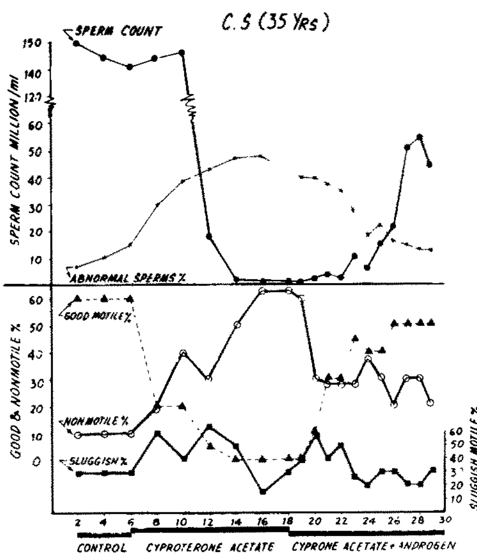

Fig. 3. Note the counteraction of cyproterone acetate-induced changes in the count, motility and morphology of the spermatozoa by concurrent administration of an androgen, mesterolone in one volunteer in Study II.

Group B. Lowest sperm counts encountered during drug therapy in this group varied from 4 to 35 million/ml, and the earliest time when the lowest count was recorded varied from the 10–22nd week. The percentage of non-motile spermatozoa reached up to 86% by the end of the 20th week, and percentage of good motile spermatozoa decreased to zero in different individuals by the 6–28th week. The variations in response in two volunteers are shown in Fig. 2a & b.

Study II

Following administration of 10 mg cyproterone acetate daily for 12–16 weeks to 3 volunteers there was a marked decrease in the count, motility and cervical mucus penetrating ability of the spermatozoa with a concomitant increase in the non-motile as well as abnormal and immature forms. The levels of seminal acid phosphatase and GPC showed a marked decrease, whereas levels of sialic acid and fructose were not significantly altered. Concurrent daily ad-

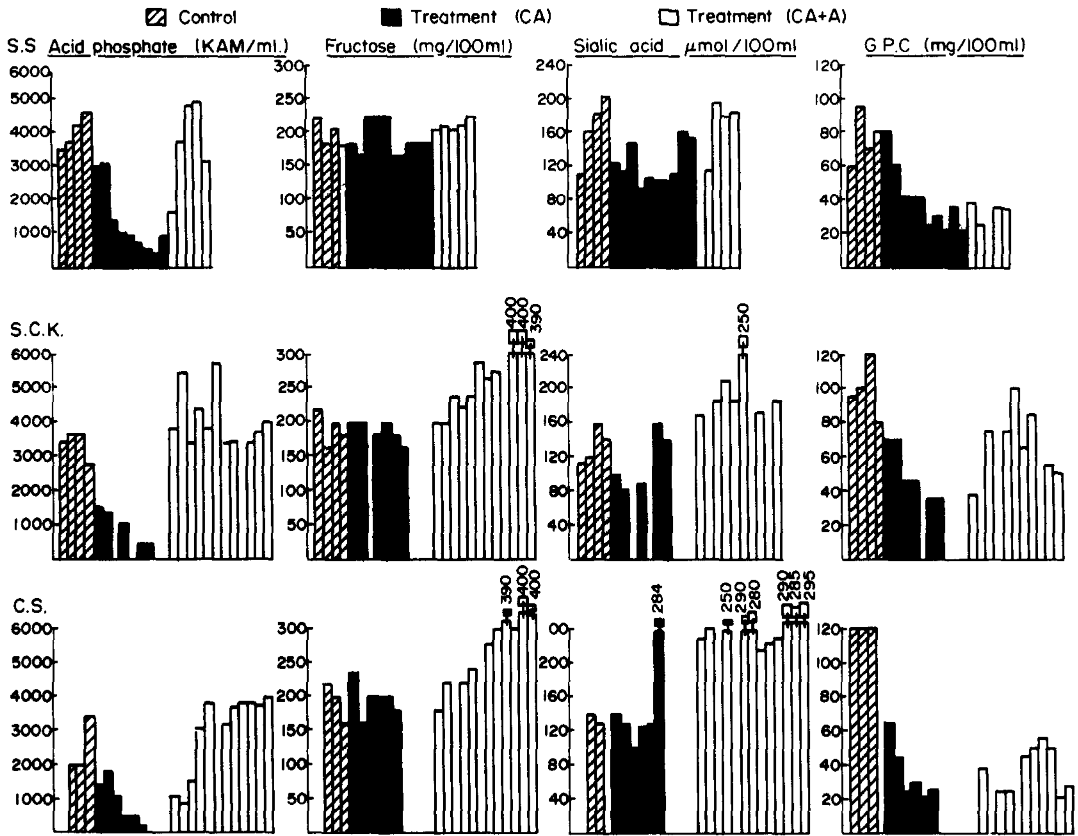

Fig. 4. Note the counteraction of cyproterone acetate-induced changes in the biochemical constituents of semen by concurrent administration of an androgen, mesterolone in three volunteers in Study II.

ministration of 75 mg mesterolone for 6–13 weeks caused a very significant increase in the count, motility and the cervical mucus penetrating capacity of the spermatozoa accompanied with a marked decrease in the non-motile and abnormal forms (Fig. 3). The sperm counts, however, were far below the control range. All the biochemical constituents of the semen were markedly stimulated during combined therapy (Fig. 4). The parameters for liver and kidney functions were not significantly altered during different drug regimens.

DISCUSSION

The results of Study I show that 10 and 5 mg daily doses of cyproterone acetate caused a significant decrease in the count, motility and cervical mucus penetrating ability of the spermatozoa and in the biochemical constituents of the semen and plasma level of testosterone, with a concurrent increase in the percentage of immotile as well as abnormal and immature forms. The decrease in sperm density, and an increase in abnormal and immature sperm cells in the ejaculate may be due to hormone deprivation at the level of the seminiferous tubules. The increase in the percentage of non-motile spermatozoa, a decrease in the ability of the ejaculated motile spermatozoa to migrate through the cervical mucus, and the decrease in seminal GPC may be explained on the basis of androgen deprivation of the epididymis. Whether or not these findings could also be attributed partly to androgen deprivation at the level of the vas deferens cannot be determined from the present study. The decrease in the levels of seminal biochemical constituents can be explained on the basis of androgen deprivation at the level of prostate, epididymis and seminal vesicles. From the changes in various parameters it is noted that low doses of cyproterone acetate did not exert any selective or differential effect on the epididymal function.

In an earlier study by Koch *et al.*[10] using daily doses of 10 and 20 mg of cyproterone acetate in human males, no significant changes in blood levels of FSH and LH were noted. However, in a more recent study using daily dose of 10 mg of cyproterone acetate and doing frequent sampling of blood Moltz *et al.*[11] have reported a 40% decrease in FSH and a 30% decrease in LH. No information is available on the possible effects of 5 mg dose of cyproterone acetate on blood levels of gonadotropins. Androgen deprivation may be brought about by this drug in two ways: (i) by decreasing the secretion of testosterone from the Leydig cells, and (ii) by counteracting the action of androgen at the level of the target tissue by competitive inhibition [8]). The decrease in the level of plasma testosterone may be produced by

partial suppression of LH secretion [11] and/or by direct inhibition of androgen biosynthesis in the testis [12].

From the results of Study II it is noted that concurrent administration of mesterolone very significantly reverted the cyproterone acetate-induced changes in the count, motility, morphology and cervical mucus penetrating ability of the spermatozoa and the biochemical changes in the semen. All these findings can possibly be explained on the basis of counteraction of androgen deprivation by androgen supplementation. However, it may be noted that the sperm counts did not return to control levels. The possible explanations for this could be: (a) mesterolone was not administered concurrently with cyproterone acetate from the beginning nor androgen therapy was long enough to bring about complete reversal, (b) combined therapy probably caused a significant decrease in FSH secretion which prevented complete restoration of spermatogenesis. Nevertheless, it is evident that the major part of the effects of cyproterone acetate was due to androgen deprivation at periferal levels.

In regard to the possible use of cyproterone acetate alone or in combination with a long-acting androgen for male contraception, further critical experimentation is needed.

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